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P. R. EVANS and I. A. B. CATHIE

CONTENTS

Chronic Maxillary Sinusitis in Children. J. F. BIRRELL 1
The Assessment of Growth and Development in Children. J. M. TANNER 10
A Familial Crisis in Congenital Acholuric Jaundice. W. N. INGRAM 34
Familial Jaundice of the Newborn Associated with Hepatosteatosis. A. HOLZEL and N. SHER 37
The Relation of Blood Pressure to Weight, Height and Body Surface Area in Schoolboys Aged 11 to 15 Years. LEO HAHN 43
Unilateral Limb Lengthening Associated with Haematogenous Osteitis in Childhood. WALLACE M. DENNISON 54
A Method of Assessing Maternal Efficiency in Socio-Medical Surveys. E. ALAN THWAITES and IAN SUTHERLAND 60
The Tryptic Activity and Presence of Cornified Squames in Meconium as an Diagnostic Aid in Congenital Intestinal Obstruction. JOHN L. EMERY 67
Fibrocystic Disease of the Pancreas with Meconium Peritonitis at Birth. F. W. [illegible] and J. F. SMITH 73
Chylous Ascites in Infancy. I. KESSEL 79
Vascular Abnormalities Associated with Pseudoxanthoma Elasticum. H. [illegible], J. F. STOKES and B. E. SCHLESINGER 82
A Case of Tricuspid Atresia with Transposition of the Great Vessels. C. F. ROSS 89
Venous Thrombosis in Acute Infantile Hemiplegia. R. G. MITCHELL 95
Lobstein's Syndrome. C. M. OTTLEY 105
Pneumonia and Empyema in Children. DUNCAN MACAULAY 107
Book Reviews 112

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CHRONIC MAXILLARY SINUSITIS IN CHILDREN

BY

J. F. BIRRELL

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(RECEIVED FOR PUBLICATION APRIL 4, 1951)

There has been a considerable volume of literature on the subject of sinusitis in childhood during the past 30 years; much of it deals with the results obtained in routine proof puncture or antral lavage. For example, Mollison and Kendall (1922) found evidence of sinus infection in 22% of 102 routine tonsil and adenoid cases. Crooks and Signy (1936) reported 24 positive proof punctures in 100 routine tonsil and adenoid cases, while Gerrie (1939) puts the percentage at 29 in 300 such patients. Carrying this further, we find that Carmack (1931) reports positive findings in 14·2% of a series of 211 tonsil and adenoid cases from which he had excluded all known sinusitic and allergic patients. There are two reports of proof puncture results in known or suspected sinus cases. Crooks (1947) found evidence of infection in 59·6% of 570 cases with opaque antra seen during 1946, while Walker (1947) obtained positive findings in 76% of 442 cases with sufficient signs and symptoms to warrant puncture out of 1,779 tonsil and adenoid patients. Lastly, Ebbs (1938) has obtained post-mortem evidence of sinus infection in 30·6% of 496 routine necropsies.

It is small wonder that sinusitis has attracted considerable attention during this period, and the importance given to this condition is reflected in the space devoted to it in StClair Thomson's book. In the second edition, published in 1916, the condition is dismissed as rare, but in the current edition, published in 1948, several pages are given to it. The implications are obvious. Ebbs' figures suggest that nearly one-third of all children suffer from sinusitis, while other reports imply that one in every four or five children requiring removal of tonsils and adenoids also needs attention to the maxillary antra. If we accept this premise wholeheartedly, we must also be willing to accept the consequences, or be prepared to explain any anomalies in the deductions arising from this premise.

The first question to be answered is how chronic sinusitis arises. It is generally conceded that, in adults at least, chronic sinusitis does not arise *per se*, but develops from an acute maxillary sinusitis in which the infected material cannot, or does not, drain away. Among adults, many more people suffer from acute maxillary sinusitis than ever develop chronic sinusitis, as most cases of acute infection return to normal. It is natural to assume that in children there will be many more cases of acute maxillary sinusitis for the same reason. Yet it is generally stated that acute maxillary sinusitis in children is an uncommon condition, and the records of the E.N.T. Department of the Royal Hospital for Sick Children in Edinburgh tend to support this opinion, as during the past five years, when over 10,000 new patients were examined, only one case of acute maxillary sinusitis was seen. How is this to be explained ? It may be that, as with acute tonsillitis, the young child makes no complaint of infra-orbital pain, accepting it as part of an acute coryza, or ascribing it to toothache. If this be so, it is possible that the great majority of children suffer from acute maxillary sinusitis, which results in one child in every three, four or five having chronic maxillary sinusitis. Or again it may be that chronic maxillary sinusitis in children differs from the adult infection by arising *per se* in the antrum. Might it not be that chronic sinusitis arises from acute sinusitis, and is not as common as one is led to believe ?

The second question to be considered is concerned with the fact that during childhood the maxillary sinus, in common with other sinuses, is in a state of active development. It grows to fill the maxilla as the teeth descend to the alveolar margin and finally erupt. If there is chronic infection lying close to these developing teeth, why is there no evidence of the eruption of unhealthy teeth, such as one finds after osteomyelitis of the maxilla ? And, again, taking as a corollary the development of the mastoid air cells, why is there no arrested aeration and growth of the maxillary air sinus ? The lack of development of a normally cellular

mastoid has been associated with the presence of otitis media in infancy and early childhood. Is one not justified in assuming that similar changes should be found in the antra of adults, and that one in every three, four, or five adults should show arrested development of the paranasal air cells, either unilaterally or bilaterally ?

Thirdly, if such a great percentage of children has been shown in the past 20 or 30 years to have had such a degree of sinusitis as to require energetic surgical correction, one must ask what happened to sinus infections in children in the past ? The treatment of otitis media in childhood is being prosecuted with zeal in the hope of materially reducing the numbers of adults with chronic otitis media. Will these energetic measures now adopted in the treatment of sinusitis in children similarly reduce the numbers of chronic sinusitis patients in 20 years ? If so, the measures will be justified, but if not, one must assume that chronic sinusitis in childhood does not persist into adult life. In other words, so-called chronic sinusitis in children must be considered a self-limiting disease, thus differing from chronic infection elsewhere. If it is self-limiting, when does it clear up, and why ? The opinion of Dean (1925) and others that removal of the adenoids and tonsils will cure 80% of cases of chronic sinusitis lends support to the theory that the natural regression of lymphoid tissue in the nasopharynx about puberty may determine this limitation of infection in the sinuses. The view is currently held in many quarters, on the other hand, that it is the sinusitis which causes and maintains the infection in, and the enlargement of, adenoids. If this view is correct, how can one explain either the disappearance of infection or the atrophy of the adenoids ? I doubt if it can be explained on this hypothesis, unless infection does not, in fact, disappear, but is really very uncommon.

The impression has been gained in the operating theatre that true chronic maxillary sinusitis is indeed uncommon, and the case notes of all the proof punctures, 240 in all, performed between January 1, 1946, and October 31, 1949, were reviewed early in 1950. Arising from these findings certain investigations have since been made, and this report is concerned, firstly, with the results obtained, secondly with the investigations, and thirdly with a discussion of the problem in relation to the literature on the subject. It should, however, be emphasized that this paper does not represent a controlled or planned investigation, but is a bald report of the findings.

One other point should be stressed at this juncture. About half-way through the period under review, it occurred to me that as these cases awaited their turn on the ordinary tonsil list, the sinus infection might have undergone resolution between the date of diagnosis and the date on which the child was sent for. Accordingly, these patients were taken out of their turn at an extra operating session so that before the end of the series cases diagnosed as sinusitis were operated upon within a week or two. The result of this procedure did not, in any material way, alter the percentage of positive results, and the series may thus be treated as a whole.

Analysis of Case Notes

Sex. Of 240 case sheets examined, 160 related to boys and 80 to girls, a ratio of boys to girls of 2:1.

Age. Only children under 12 years of age are admitted to this hospital, and the ages are shown in the accompanying graph. It will be seen that

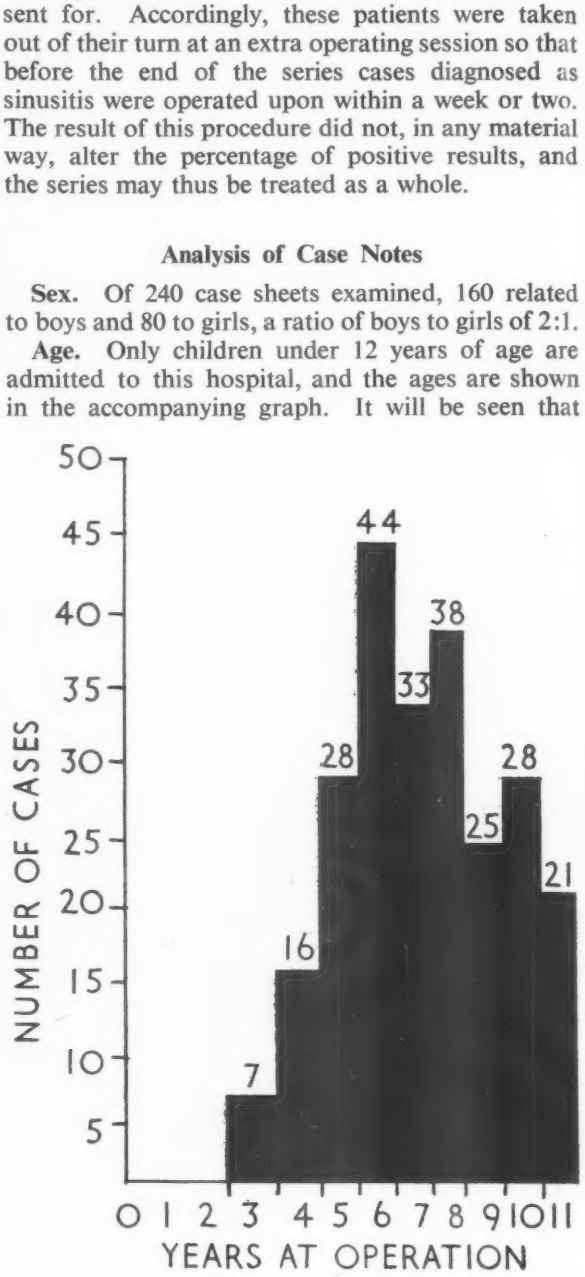

FIG. 1.—Graph showing age at puncture.

there is a preponderance of children in the 6-8 years age group. This is the age at operation, and the preponderance of this age group would be even more marked if cases were examined at the age at which sinusitis was diagnosed, as many of the

9 to 12-year-old children had waited up to two years for admission.

Symptoms. It is very difficult in a review such as this to obtain an accurate picture of the presenting symptoms, as case histories have been taken by a number of different people—by residents, out-patient sisters, secretaries and surgeons. There is thus no unanimity of view, as would be obtained in a planned investigation, such as that of Birdsall (1939).

For what they are worth, the following symptoms have been noted: nasal catarrh, nasal discharge, or running nose (60 cases); frequent colds (40 cases); nasal obstruction or mouth breathing (35 cases); persistent cough (23 cases); bronchitis (10 cases); bronchiectasis (11 cases); headaches (19 cases); asthma (22 cases); hay fever (one case); allergic rhinitis (one case); discharging ears or deafness (27 cases); laryngitis (five cases); pharyngitis (one case); epistaxis (two cases); night sweats (one case); and acidosis (one case). In 39 case sheets there was insufficient history for the predominating symptom to be listed.

Signs. On examination of the nose, the findings have varied with the descriptive power of the examiner, and I have aggregated these into groups as follows: nose clear, i.e. a dry nose with no swelling of the turbinates (58 cases); congested nose (17 cases); allergic type of nose, i.e. pale, swollen turbinates (35 cases); nose containing unspecified discharge (50 cases); mucoid discharge (four cases); mucopurulent discharge (19 cases); purulent discharge (29 cases); crusted discharge (21 cases); and deflected septum (15 cases). No notes were made on eight case sheets.

Tonsils and Adenoids. Tonsils and adenoids were present in 117 cases, and had been removed in 117 cases. In the remaining six case sheets there are no notes. When tonsils and adenoids were present, their removal was carried out at the same time as the puncture in 42 cases. Of the patients whose tonsils had previously been removed, tonsillectomy was deemed inadequate in nine cases. Thirty-four patients were recommended to have adenoids (either the primary growth or the recurrence) removed at the same time as the puncture, and this is distinct from the 42 tonsil and adenoid operations listed above.

Radiology. Positive radiological findings were obtained in every case subjected to proof puncture, and no case was clinically labelled sinusitis until a radiograph revealed either mucosal thickening or opacity of the antrum. This aspect of the diagnosis will be discussed in greater detail later.

Technique. The children were all dealt with as in-patients. After pre-operative luminal the child was anaesthetized with ethyl chloride vapourized in a Guy's inhaler. No local cocaine anaesthesia was used. An opportunity was thus afforded of palpating the nasopharynx and removing any adenoid mass requiring surgery, and palpation and curettage is now part of the routine procedure of a proof puncture.

A Lichwitz trocar and cannula were used, and sterile saline solution injected into the antrum from a 5 ml. syringe carrying a blunt-pointed needle inserted through the cannula. A 2-3 ml. quantity of the solution was injected into the antrum, the head being rolled through 45° to the corresponding side. The solution was then reaspirated into the syringe and examined macroscopically for mucopus or pus. If this were present, further wash-outs of this kind were used, or a Higginson's syringe was attached to the cannula, and the classical wash-out employed. With this injection and reaspiration technique no accidents have occurred. This method is thought to be the only accurate means of determining the contents of an antrum, as the simple antral wash-out, without preliminary injection and aspiration, carries with it all secretions lying in the nasal cavities and nasopharynx, and, indeed, in bronchiectatic subjects, much pulmonary secretion is added to the specimen during the cough associated with recovery from anaesthetic. No reliance can be placed on the antral wash-out as a diagnostic guide. It is a therapeutic measure alone.

Results

One hundred and forty-two double punctures were carried out. The right antrum alone was punctured 51 times, and the left on 47 occasions. Thus, the 240 cases represent 382 punctures. The results are shown in Table 1.

Resolving the double proof punctures to single ones, the total number of antra in which pus was

TABLE 1
240 CASES REPRESENTING 382 PUNCTURES

	Pus	Muco-pus	Nega-tive	Total
Double proof puncture ; same reading in each	8	2	109	119
Double proof puncture ; left negative ; right	7	7		14
Double proof puncture ; right negative, left	5	4		9
Right proof puncture	5	1	45	51
Left proof puncture	3	1	43	47
Total	28	15	197	240

found is 36, and the total number showing mucopus is 17, while a total of 329 antra gave a negative result. That is to say, 9·42% of the antra contained pus, and 4·45% yielded mucopus. These results were found in a series of cases diagnosed clinically and radiologically as chronic sinusitis, and are not a series of routine punctures.

Analysing these results with respect to the symptoms and signs, two things must be borne in mind. In the first place many children had more than one symptom or sign, and this means that the result is marked opposite each. For example, a child with bronchiectasis, giving a history of frequent colds, who had pus in one antrum, would have the result shown against each of these symptoms. The second point to be noted is that the numbers in these tables refer to cases, *not* punctures, so that a bilateral puncture is shown as one case. The results are correlated with symptoms in Table 2, with signs in Table 3 and with the presence or absence of tonsils and adenoids in Table 4.

TABLE 2
RESULTS CORRELATED WITH SYMPTOMS

	Pus	Mucopus	Negative	Total
Nasal catarrh	10	3	47	60
Frequent colds	4	2	34	40
Nasal obstruction	1	2	32	35
Persistent cough	0	2	21	23
Bronchitis	1	0	9	10
Bronchiectasis	4	1	6	11
Headaches	2	3	14	19
Asthma	3	1	18	22
Hay fever	0	0	1	1
Allergic rhinitis	1	0	0	1
Otorrhoea or deafness	2	3	22	27
Laryngitis	0	1	4	5
Pharyngitis	0	0	1	1
Epistaxis	1	0	1	2
Night sweats	0	0	1	1
Acidosis	0	0	1	1
No notes	3	2	34	39

TABLE 3
RESULTS CORRELATED WITH SIGNS

	Pus	Mucopus	Negative	Total
Clear	3	4	51	58
Congestion	4	0	13	17
Allergy	1	0	34	35
Discharge, unspecified	6	3	41	50
Mucoid discharge	0	1	3	4
Mucopurulent discharge	2	3	14	19
Purulent discharge	10	1	18	29
Crusted discharge	3	1	17	21
Septal deflection	1	1	13	15
No notes	0	3	5	8

A correlation of the results with symptoms and clinical features offers no striking solution, and no statistical analysis has been attempted in view of the lack of standardization in note-taking and examination. The first result calling for comment is that less than one-fifth of the cases suffering from ear trouble gave positive proof puncture findings. This surprised me, as I felt that chronic sinus disease played a larger part in maintaining ear trouble in children.

The other significant fact is that five of the 11 bronchiectatic patients had a positive puncture.

TABLE 4
RESULTS CORRELATED WITH PRESENCE OR ABSENCE OF TONSILS AND ADENOIDS

	Pus	Mucopus	Negative	Total	
Tonsils and adenoids present	10	5	60	75	117
Tonsils and adenoids with puncture	3	3	36	42	
Tonsils and adenoids removed	14	4	90	108	117
Tonsil remains present	0	1	8	9	
Adenoids removed with puncture	1	1	32	34	
No notes	0	1	5	6	

This might be allied to the report of positive findings in 11 of the 29 patients showing pus in the nose on clinical examination. The association between chronic sinus infection and bronchiectasis is well recognized (Hogg, 1950). In all four cases of bronchiectasis with pus in the antrum, the nose showed purulent secretion, but, on the other hand, pus was present in the nose of two other patients suffering from bronchiectasis, in each of whom a bilateral puncture gave negative results.

There appear to be no other coincidences in the series, and one does not, therefore, seem justified in making any forecast of the probable result of proof puncture from an assessment of the symptoms and clinical signs. Nor, indeed, has experience shown that any reliable evidence can be obtained from radiographs. Positive and negative results have been found in cases whose radiographs show complete antral opacity or gross mucosal thickening. The appearances are not as diagnostic as in adults, for in children the results are confused by the growth of the antra, which are often shallow, and by the lack of air entry, either due to enlarged turbinates, enlarged adenoids, secretion lying in the nose, or habitual mouth breathing. The confusion in assessing radiographs was apparent in the cases of two children of the same age, both showing pus in the nose and both suffering from bronchiectasis, who had bilateral punctures performed on the same morning. The radiograph of one showed bilateral antral opacity, the other showed a moderate degree of mucosal thickening. The child with complete antral opacity had a bilateral negative puncture, while the other, with mucosal thickening, showed pus in each proof puncture !

Follow-Up

The punctures were repeated in the positive cases at an interval varying from one week to one month from the time of the initial puncture. The results of this puncture showed that four cases still produced pus in an antrum. Of these, two cleared up at further puncture, but two remained positive after repeated punctures and these were drained intranasally. Thus only two of the 382 in the series did not clear with proof puncture, and for this reason only these two might be said to have suffered from irreversible chronic maxillary sinusitis, a percentage of 0·53%.

Discussion

These results do not bear comparison with those quoted in the literature. To find mucopus or pus in the antra of only 13·9% of a series of patients diagnosed clinically and radiologically as cases of chronic sinusitis compares strangely with the 59·6% of Crooks (1947) and the 76% of Walker (1947). The obvious explanation is that the latter figures are those of antral wash-outs, and not of proof punctures.

Walker describes his operation as antral lavage, and Crooks, who quoted his figures during a discussion on a paper by Archer (1947), uses the expression ' washed out ', though his earlier paper (Crooks and Signy, 1936) carefully described how the antral contents were aspirated. It has been explained that an antral wash-out is not a diagnostic test, and Walker's statement that the nose was blown on the morning of operation can hardly be taken as proof that abnormal secretions did not remain in the nasal cavities or nasopharynx. The average child is singularly unable or unwilling to clear the nose by blowing.

The problem of finding diagnostic criteria on which to pronounce a given sinus to be infected with any degree of certainty is, to my mind, an extremely difficult one. Dean (1925) thought diagnosis was easy, and other writers, such as Birdsall (1939) and Walker (1947), appear to rely on symptoms, signs and x-ray findings in their assumption that a child has sinusitis.

In most articles mention has been made of radiological findings, and I have stated above that all the cases dealt with in this series had preliminary radiological evidence of antral opacity or of mucosal thickening, though those appearances bore no relation to the actual results. The earlier the paper, the greater appears to have been the faith in radiography. Cleminson (1921) considered radiographs valuable, while Dean (1925) stated that 'the greatest benefit to be derived from roentgen-ray examination is to tell us whether or not a given sinus is present, and, if present, whether on an anatomical basis, it has clinical significance '. Crooks and Signy (1936) judged radiography to be ' the most sensitive of all the diagnostic tests ' because it ' will show slight and transitory changes of mucous membrane '. They go on to say that radiography may be misleading if it is not correctly interpreted and correlated with the clinical condition. They found, however, that it was common to wash out an antrum which was opaque to x-rays, and yet obtain a clear return, and concluded that the antrum is diseased none the less, but is draining adequately. I confess that I find it difficult to follow this argument in the light of my own experience, and I tend to agree with Macbeth (1950) who believes that radiographs are of no use in determining the nature of mucosal changes in children.

Bowen-Davies (1938) made a bacteriological study of the results obtained in puncturing the antra of 55 children, and his results are rather astonishing.

Of the 110 antra, 66 appeared, from x-ray examination, to be infected. Of these, 27 were proved to be bacteriologically unhealthy, and 39 were sterile. His conclusion is: ' It appears, therefore, that when the skiagram is positive the antrum will probably be sterile.' Of the 44 antra with negative radiographs, 35 were sterile and nine were infected, and his conclusions are: ' It is therefore probable that an antrum which appears normal on x-ray will be sterile, but there is a possibility (one in five) that it may prove to be infected.' Bowen-Davies assesses radiographs as of little use in diagnosing infection in children.

If one cannot rely on a correlation of clinical and radiological features to diagnose with accuracy chronic sinus infection in children, one's thoughts turn to other diagnostic criteria of infection. Carmack (1931) has studied the blood picture in a series of cases, and he finds a moderate increase in white blood corpuscles, a decrease in the red cells and a low haemoglobin level. The blood chemistry is normal. These findings do not suggest that any assistance is to be had from a routine examination of the blood.

One of the investigations which leads one to suppose chronic infection to be present in the body is a high erythrocyte sedimentation rate. More recently we have been doing routine E.S.R. readings on proof puncture cases, but after obtaining such confusing results as bilateral thick pus in a child with an E.S.R. of 6 mm. in the first hour, and a bilateral negative puncture in a child whose E.S.R. was 22 mm. in the first hour, as well as a host of other results showing no definite trend of correlation, the procedure has been abandoned as a diagnostic aid.

Then a series of cases was investigated in the hope that one might explain the clinical and radiological findings on the basis of nasal allergy. It was not thought practicable to remove portions of mucous membrane for biopsy under the same anaesthetic (ethyl chloride) as served for the puncture and attention to tonsils and adenoids. Nor did we consider ourselves justified in turning the procedure into a major operation by having the child intubated for this purpose. Accordingly, nasal swabs were taken and examined for eosinophils with conspicuous lack of success, and the conclusion reached was that nasal allergy was not the explanation of the negative punctures in radiologically positive cases.

It would appear, therefore, that there is no means at present of diagnosing with any degree of certainty the contents of an antrum in childhood. One cannot foretell the cases in which pus or mucopus will be obtained at proof puncture. It therefore follows that, in order to avoid missing the few cases with evidence of infection in the antrum, every patient showing antral abnormality on radiographs must be proof punctured, and, until a reliable diagnostic criterion is discovered, this wholesale puncturing of antra must be continued as the only means of establishing diagnosis.

Children are apprehensive of anaesthetics, especially ethyl chloride, and of manipulations without general anaesthesia, and we should therefore be able to treat the occasional antrum showing pus at the same time as we arrived at the diagnosis. It appears from the results quoted above and from those of other writers that the vast majority of antra clear up after a single antral wash-out, and for this reason any antrum showing pus on aspiration has the sinus flushed out. Again, many authorities believe that the removal of tonsils and/or adenoids is essential to the cure of sinus infection, so to complete the cure these should be dealt with at the same operation and under the same anaesthetic.

The only author opposed to antral wash-out is Scott Stevenson (1947) who thinks that it causes otitis media. He agrees with Dean (1925), Cleminson (1921), Mollison and Kendall (1922) and Carmack (1931), among others, in advocating the removal of the adenoids, asserting that he has never seen a case of maxillary sinusitis in childhood in which the adenoids were not present, even when they were supposed to have been removed. This agrees with the experience of most operators, except Walker (1947) who found the tonsils more blameworthy than the adenoids, and assessed their degree of involvement by their actual size.

There is unanimity that most sinusitis in children can be cured by antral wash-out, with or without the removal of tonsils and adenoids, but, if this is so, was the sinusitis treated really chronic or irreversible, as it is currently described, at the time ? Or was there merely some infected material which happened to be in the sinus ? Crooks and Signy (1936) have declared that in the cases where a negative puncture appears to confound the radiological appearance, the sinus is actually infected, but is draining well. In view of the number of negative punctures in this series, I wonder whether those cases with transient pus or mucopus are not really cases of nasal catarrh where the sinus is draining poorly, and whether indeed the two antra persistently positive were not the only cases of true sinusitis in the whole series ?

Conservative measures advocated for the treatment of sinusitis include change of climate to the seaside (Dean, 1925; Crooks and Signy, 1936), Proetz displacement (Birdsall, 1939; De Boissière, 1949) and x-radiation (De Boissière, 1949). Dietetic therapy is recommended by Dean (1925), and this should include a liberal supply of vitamin A.

Dietetic errors, especially excessive carbohydrate intake, have been mentioned by Scott Stevenson (1947) as combining with improper ventilation of the home to produce catarrhal changes. Macbeth (1950) uses postaural nasal soaks of freshly mixed penicillin, albucid and tuamine sulphate. The antibiotics may be instilled into the antra through indwelling catheters (Archer, 1947; Harpman, 1947) or polythene tubing (Hogg, 1950). Bateman (1945) suggested a paste of penicillin, flavazole and soluthiazole in lanette wax or concentrated plasma solution to the consistency of honey for use in adults, and Harpman (1947) comments on its use in children.

Should conservatism fail, or minor surgery not result in a cure, recourse is had to antral surgery. The operation of current choice appears to be the Caldwell-Luc or radical antrostomy (Crooks, 1947; Harpman, 1947; Scott Stevenson, 1947; Macbeth, 1950, and others) though Crooks in 1936 recommended intranasal drainage. Admittedly only a small percentage of cases required this operation, and it was only resorted to when other methods failed, but it seems a serious operation to undertake in a child of 4 years of age, the case reported by Harpman. At the Caldwell-Luc operation, it is reported that the mucosa shows changes in no way inferior to the changes found in adults with chronic sinus suppuration (Crooks, 1947). Yet an investigation by Bowen-Davies (1938) showed that while the average time of elimination of lipiodol from the antra in sterile cases was 17·9 days, the average time of elimination in infected cases was only 14·9 days. He explains this by the fact that there is reduced capacity in these antra, due to mucosal encroachment, but the function of the cilia is not disturbed by infection. It seems rather a radical procedure to remove ciliated epithelium which is performing its function normally.

This is the general picture of the approach to the problem in the country today, but I must confess to a certain scepticism. It appears that many of the deductions made arise from the assumption that sinusitis is an extremely common condition in children (Guthrie, 1939), an assumption which does not appear to me to be warranted. I would hardly go the length of Hajek whom Crooks and Signy (1936) quotes as saying: 'The fantastic reports of some American authors . . . who describe an enormous number of empyemas observed in the earliest years of childhood . . . are to be regarded with the greatest suspicion, as their methods of examination give no assurance of the reliability of their results.'

The articles from which I have quoted in this paper were written by eminent authorities, and their methods are described in considerable detail. Because their results differ widely from those which have been obtained in Edinburgh, it does not necessarily follow that they are wrong. Indeed, the results of my series bear no comparison with any other published figures, except those concerning the Carmack (1931) series from which he had excluded all known sinus and allergy cases.

One criticism which has been made in discussing this series with some of my colleagues is that no bacteriological examination was made of the aspirated fluid, and thus many cases have been labelled negative which were really positive. The obvious retort is that mucopus or pus is the diagnostic criterion of infection, and that one can grow bacteria from many surfaces in contact with air even when these surfaces are not infected. A glance at the literature will confirm the confusion of thought in this criticism. Crooks and Signy (1936) found the same organisms, admittedly in differing proportions, in positive and negative punctures, and Bowen-Davies's (1938) bacteriological conclusions from his series complicate the picture still further.

The literature leaves us with the impression that chronic maxillary sinusitis is a common condition which affects one in every three, four, or five children, but which cannot be diagnosed with certainty by clinical findings, blood examination, E.S.R. readings, radiography, or bacteriological results from proof puncture, and this condition must be treated by removing adenoids and tonsils, by antral wash-outs, indwelling catheters for antibiotics, or, if all else fails, by a Caldwell-Luc operation, even though the ciliated lining of the antra is functioning normally.

The more one reads about this confusing subject, the more one wonders whether there is really any such disease as chronic sinusitis, or whether the symptoms and signs might not be explained by some other mechanism. There is no doubt that the sinus mucosa in a child is capable of considerable swelling, and that this swelling may persist for a time. There is also no doubt that children are susceptible to repeated acute infections of the upper respiratory tract, resulting in mucosal swellings. To get adequate drainage and resolution, ventilation of the sinus is necessary, but is prevented by blockage of the airway through the nasal cavity. The blockage in turn is augmented by a swelling of the mucosa of the turbinates, so that a vicious circle is set up, the swollen mucosa blocking the nasal airway and the lack of ventilation interfering with shrinking of the nasal and sinus mucosa. Thus, as from enlarged adenoids, habitual mouth-breathing develops. In time the nasal mucosa may settle, but each succeeding acute infection prolongs the time, and once mouth-breathing is established, sinus ventilation

remains impaired, and the sinus mucosa remains thickened.

The reason why removing tonsils and adenoids helps these cases is not so much that infection is eliminated, as that, after removal, there is an increased chance that nasal respiration will be resumed, especially during sleep. If the child's room is well ventilated during the night, nasal breathing should be restored, but if there is insufficient fresh air, catarrh and mouth-breathing may persist. This would serve to explain why the greatest percentage of so-called sinusitis cases are found in the 6 to 8 years group, for this period embraces the physiological enlargement of tonsils and possibly of adenoids. Such enlargement will cause a sense of stuffiness, quite apart from the superadded acute infections.

Secretion lying in the nose, which the child is not taught to blow out properly, further impedes airway. The discharge is either present at the anterior nares, from which it is wiped, not blown, or is continuously sniffed backwards, and the nose is never completely cleared.

If one accepts these facts, it serves to explain why so many so-called sinusitis cases are relieved by removing tonsils and adenoids, by Proetz displacements, by mechanical douching, or antral lavage. It also serves to explain why no reliance is to be placed on clinical features, radiographs and proof puncture results. No sinus can remain free from secretion when the nasal cavity, with which it communicates, contains a plentiful supply of secretion. A certain amount will undoubtedly escape back into the nose from the antra, but some may be left in place, and would explain the paradoxical statement that the sinus is infected, but is draining well. The sinus is not infected. It merely receives a certain amount of spillage from the nasal cavity, and the cilia get rid of this quickly against an obstructed ostium. How much more easily would the cilia deal with the secretion if the nose were properly aerated and cleaned.

The correct way to aerate a nose is not to use vasoconstrictor drops or sprays, nor to douche it out via the antrum each week under local or general anaesthesia, but to train the child in nose-blowing and nose-breathing. No quantity of ephedrine and no multiplicity of wash-outs will ever clear the nose of a child who is afraid to use it for breathing. One constantly meets children who have a clear nasal airway, free from secretion, and whose adenoids and tonsils have been adequately removed, but who approach panic when told to close their lips and breathe through their noses. It is ten times worse in those whose adenoids are present, and whose noses, lined by swollen mucosa, are filled with secretion.

In a discussion on an upper respiratory clinic for children held at the Royal Society of Medicine in 1945, Gwynne-Evans (1945) showed radiographs demonstrating how the failure of the palato-lingual reflex to close the faucial isthmus resulted in mouth-breathing, while an active palato-lingual reflex preserves nasal respiration. But the radiographs also showed that the antra were hazy in the child who breathed through the mouth, and clear in the child who used the nose for breathing.

In the same discussion Nove (1945) mentioned that relaxation of lingual musculature resulted in a low level of the hyoid bone, and stated that this was associated with mal-related jaws, post-nasal catarrh and respiratory abnormalities. After orthodontic treatment the tone of the muscles improved, the hyoid assumed its normal level, and the tongue ceased sagging. This resulted, among other things, in an improvement in respiration. Again, the radiographs showed blurring of the antra before treatment, and clear antra thereafter.

These two papers lend unwitting weight to the theory that the clinical and radiological appearances of sinusitis in children may be found with mouth-breathing, and will disappear when nasal respiration is established. If, then, we disabuse our minds of the idea that chronic sinusitis in children is common, though undiagnosable, and search for one factor which will produce all the signs and symptoms associated with the condition, we find the answer in mouth-breathing. The treatment, therefore, should not be directed against a non-existent sinusitis, but against mouth-breathing. The children and their parents must be taught the importance of using the nose for its proper function. The children must be shown that it is possible to breathe adequately with the lips shut. Physiotherapists may have to issue the initial instructions on breathing exercises, and I venture to think that if these exercises are continued until nose-breathing has become unconscious, the clinical features will disappear. It may be necessary to remove adenoids and tonsils in the first instance, and to use drops of 2-5% argyrol to reduce any rhinitis, but these may be quickly dispensed with, and the dying habit of ' nose-drill ' continued.

In this way we may find that the so-called chronic sinusitis is really as uncommon as acute sinusitis in children, and that the figures of 0·53% of all so-called sinusitis cases is a correct one.

Conclusions

The results of 382 proof punctures in 240 children, clinically and radiologically diagnosed as chronic sinusitis, showed positive results in 13·87%, but

only two children (0·53%) were considered to be true cases of chronic maxillary sinusitis. An examination of the literature in conjunction with these results leads one to the conclusion that the condition cannot be diagnosed with accuracy by any means at our disposal. It is felt that the generally accepted theory that sinusitis is common in children is false, and does not withstand critical examination. If the problem is approached with an unbiased mind it will be appreciated that identical clinical and radiological findings may be produced by habitual mouth-breathing. Treatment should be directed in the first instance towards re-establishing nasal respiration rather than against a non-existent sinus infection.

A proportion of the cases reported in this paper were punctured by my senior colleague, Dr. C. E. Scott, to whom I am indebted for permission to include them in the series.

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THE ASSESSMENT OF GROWTH AND DEVELOPMENT IN CHILDREN

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During the last decade or two, as part of the general application of preventive medicine to human affairs, an increasing interest has been taken in the growth of children. To a large extent this followed the realization on the one hand that malnutrition could cause a retardation of growth in the child, and on the other, that differences in size did actually exist between children belonging to different social classes. From this it was a short step to the assumption that the rate of growth itself afforded an index of the nutrition, or at least of something called the ' general condition ' of the child; and on this premise, both in relation to groups and to individuals, paediatricians, public health officers and the School Medical Service began to take regular measurements of the children under their care. Having got the measurements it was necessary to have something with which to compare them, and standard figures from supposedly good samples of supposedly healthy children were soon forthcoming. The Baldwin-Wood tables, for example, a 1923 revision of figures first published in 1910, were widely used for a time and found their way into many textbooks of paediatrics. Alongside the salutary results of all this activity, two bad effects were clearly to be seen. When standards were first published what is implied by ' the spread of the normal ' and ' the limits of the normal zone ' was not at all generally understood. Anxious parents, consulting the oracular weighing-machine, plagued their practitioners with complaints of their children being five pounds under- or over-weight for their height and age, and this despite both mother and father being miracles of thinness or rotundity. Also it began to be quite uncritically assumed that the faster you grew the better it was, and since the more you ate the faster you grew—particularly in weight—an era of stuffing babies and children regardless of all psychiatric or humanitarian principles began. Only recently have any voices been raised against this trend, but there are signs that these are now making themselves heard, and animal evidence on feeding and longevity (Ball, Barnes and Visscher, 1947), though probably not strictly relevant, will doubtless help to redress the balance.

Meanwhile, more and more standards have been published, most using height and weight combined with other anthropometric measurements and some, in addition, assessments of maturity by hand, radiograph or bodily appearance. The situation has grown somewhat confusing and a general clarification would seem useful at the present juncture. It is the aim of this paper, therefore, to give a coherent account of the standards in use and the principles on which they are constructed, using language as non-technical as is possible without shirking the issues involved. It is foolish to pretend that any of the methods so far proposed are ideal or even very satisfactory, and the reader must not imagine that at the end he will emerge with a finally chosen foolproof, automatic system for use on all occasions: it is hoped, rather, that he may be brought to a clearer conception of the methods at present available, the foundations on which each is based, and the uses to which each can and cannot be put. A new arrangement both for graphing and reporting growth progress is suggested in Figs. 5 and 8, but the suggestion is a tentative one requiring practical test, and the arrangement is certainly not as suitable for some periods of growth as for others: at puberty, for example, it seems likely that some slight complications will have to be introduced if the precision of the standards is to be maintained.

The paper is divided into sections: the meaning of abnormal; percentiles versus standard deviations; distance versus velocity standards; distance standards available (measurements considered singly); use of distance standards for assessing

velocity; multiple measurement distance standards; a suggested form for combined distance, velocity and standard-score difference standards; standards for maturity; conclusion.

The Meaning of 'Abnormal'

The point of any standard of whatever sort is to enable the physician, nurse or whoever it may be to give at least a tentative answer to the question, 'Is this child abnormal?' If the answer is no, the anxious mother is reassured; if yes, further steps are taken to eradicate or minimize the abnormality, and to remove, if possible, its source. But this question is not quite as simple as may appear at first sight and we must begin by getting clear in our minds just what the question implies and just what sort of an answer it is possible to give.

We shall consider in this section only one single measurement; let us say of stature. If we measure a very large number of 6-year-old children, all healthy so far as we know, we shall find a few short ones, a few tall ones and a lot of middling height. If we plot a graph of the number of children along the y axis against stature along the x axis we will have a series of points, and if we join these by a smoothed curve we shall have the frequency distribution curve illustrated in Fig. 1A and 1B; this is a Gaussian or normal curve of distribution. In Fig. 1A a series of vertical lines have been put in, delimiting the percentiles of the distribution; by this is meant that 1% of the population are smaller than the stature given by the vertical line marked 1, 2·5% are smaller than the stature given at the line 2·5, and so on. For this sort of distribution curve the mean stature of the group and the 50th percentile coincide; just half the population are below the mean stature and half above it. Now if we have a 6-year-old child M we can immediately compare his stature to that of this standardizing population by seeing which percentile on the figure he lies nearest. If his stature is the same as that of the 95th percentile we can say that only 5% of healthy children of this age are taller than M. If it lies at the 99th percentile, only 1% of healthy children are taller. If M is as tall as this then obviously the suspicion is aroused that he is 'abnormally' tall; in other words, that he is not really a member of this healthy population to which he is being compared, but of another, unhealthy population.

Now suppose we have a second group of children, all of whom have acidophil adenomata of the pituitary, mid-brain tumours and so forth. This is the abnormal population, and on average its members will be taller than the members of the normal population. But the two populations may overlap in distribution, and we then get the situation hypothetically illustrated in Fig. 2; in general the unhealthy population is likely to be a mixture coming from various causes of ill-health with varying effects, producing a frequency distribution which is not Gaussian and has a large scatter. We can now return to child M, stature at the 99th percentile, with a clear idea of what we mean by affirming or denying that he is abnormal. Since the populations overlap in this region it is not possible to say with certainty that M belongs to one or to the other. All we can state is the probability of his belonging to one or the other, and this probability we can state precisely if we know the distributions of the two populations. In practice we usually do not know the distribution of the unhealthy population and we lay down arbitrary 'limits of normality'. It is essential to recognize that these are arbitrary, and to understand what they imply. Suppose we take the stand that anybody over the 95th percentile shall be called 'abnormally tall'. Most, perhaps, of the actually abnormally tall would be picked up by this procedure, but at the expense of including in this category five out of every 100 normal children. If we adopt the 99th percentile as the limit, then we may pick up fewer real abnormals, but we shall only call one normal person in every 100 abnormal. The limits of normality we should adopt must depend on the use to which they are going to be put; if the result of being classified as abnormal was immediate and serious operation, we should have to put the limit even beyond the 99th percentile, to ensure we operated on very few normals, but if stature is being used as a first screening test for suspected malnutrition, say, with a result nothing more drastic than a visit to the specialist and some extra milk in the mornings, our limits could be much lower, perhaps even at the 80th, or in this particular example, its lower equivalent the 20th, percentile. This sort of problem, though stated here in somewhat academic terms, arises acutely sometimes in paediatric practice, as, for example, in whether or not to explore for a possible tumour in a girl who begins to menstruate somewhat earlier than usual.

Percentiles versus Standard Deviations

Standards of growth in current use employ either the percentile division outlined above or else a division of the healthy population by standard deviations* (e.g. Sontag and Reynolds, 1945). In

* The standard deviation (σ) is a measure of the spread of a frequency distribution. It is particularly appropriate to Gaussian distributions, in which the correspondence of various multiples of σ to various percentiles can be seen from Figs. 1A and 1B. It is estimated from a sample of readings as the square root of the sum of the squares of the deviations of the readings from their mean divided by one less than the number of readings.

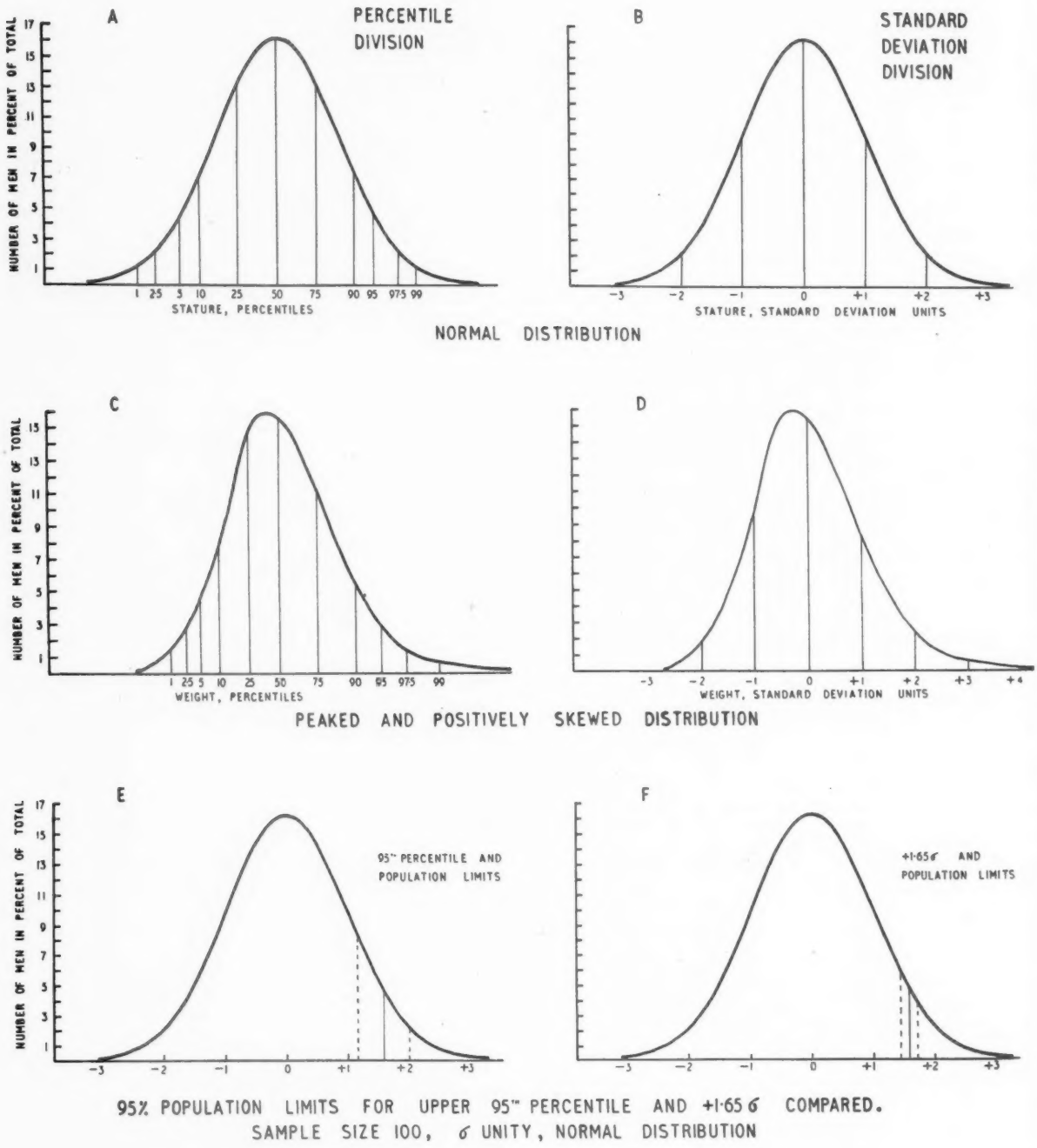


FIG. 1.—To illustrate the relation of percentile and standard deviation divisions of A and B a normally distributed population, C and D a peaked and positively skewed distribution. E and F show the sampling limits of the upper 95% point in a normal distribution.

the latter case, the standard deviations are used essentially as percentiles (see Fig. 1); the given child's stature is found to be greater than the mean by a certain figure and this figure is so many, say, 2·3, standard deviations (σ). By reference to a table of the Gaussian curve it is found that only 1% of the

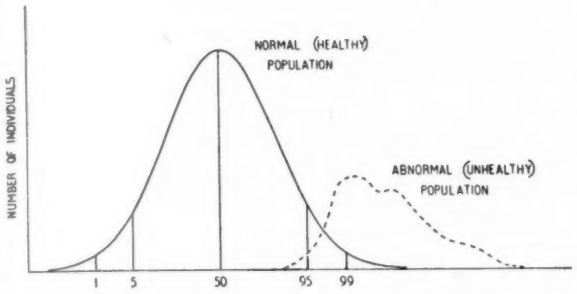


FIG. 2.—Possible overlap of a healthy and unhealthy population (hypothetical).

population are taller than 2·3σ above the mean, and the interpretation and the laying down of limits proceeds as before. In other words, provided the population distribution is Gaussian, as in Fig. 1A and B, +2·3σ corresponds to the 99th percentile, −2·3σ to the first percentile, +1·65σ to the 95th percentile, −1·65σ to the fifth percentile, and ±0·67σ to the 25th and 75th percentiles.

This reasoning, however, breaks down if the distribution of the healthy population for some measurement is not Gaussian, but skewed, as in Fig. 1C and D. Here a distribution curve similar to that usually found for body weight is given; it is not Gaussian, but has a higher peak and a longer tail out to the right. (Weight, it may be noted, is the most highly skewed of all the commonly used measurements with the exception of subcutaneous tissue thickness; most length measurements have Gaussian distributions, and breadths, depths and some circumferences tend to be a little skewed in the same direction as weight.) In such a skewed distribution percentiles can still be drawn in, as in Fig. 1C, though the 50th percentile no longer corresponds either to the peak of the curve or to the value of the arithmetic mean. But as can be seen from Fig. 1D the standard deviations no longer correspond to the same percentiles as for the Gaussian curve. We can no longer say that a child of +2·3σ is exceeded in weight by 1% of the healthy population; clearly he is exceeded by more. Thus the use of standard deviation divisions is fraught with errors of interpretation unless the population distribution is Gaussian.

There are, however, two advantages in the use of standard deviations rather than percentiles. First, there is the relatively unimportant one that the presentation of standard data is simplified; all that need be given is the mean and the standard deviation, the table of the Gaussian curve for passing from standard deviations to percentiles being in any book of elementary statistics. Secondly, there is a more telling advantage of a biometrical nature. All the standard data published are data on samples of healthy children, not the complete measurements of every healthy child in the country (let alone the extra ones needed by the mathematicians to make their population infinite). Most of the samples consist of a few hundred children at each age; the published standards, however, are for the whole healthy population. We find the 95th percentile for our sample, and from this estimate the 95th percentile for our whole population. The estimate is subject to a certain amount of error; all we can say with confidence is that the population 95th percentile lies between the two limits illustrated in Fig. 1E by the two vertical interrupted lines (unless we have been so unlucky as to have struck a sample which would only occur less than five times in 100, in which case the population value will lie actually outside these limits). In the same way we can calculate the standard deviation from our sample and estimate the 95th percentile of the population as 1·65 standard deviations, but in this case the limits between which our population figure is fairly sure to lie are much narrower, provided the distribution is Gaussian. This is illustrated in Fig. 1F; compare the position of the vertical interrupted lines with Fig. 1E. Looked at another way, it requires more children in the standardizing sample to estimate the percentiles for the population to a given degree of accuracy than it does to estimate the standard deviation. In fact, it needs, in a Gaussian distribution, just four times as many to estimate the 95th percentile with the same accuracy as the 1·65σ level, and 14 times as many to estimate the 97·5 percentile with the same accuracy as its corresponding 2σ level.

The question can be summed up thus: if the distribution of the measurement is Gaussian or very near it, then standard deviation divisions and limits of normality are preferable. But if the distribution is non-Gaussian, then percentile division has to be used since the standard deviation method will not locate the point required; in technical language, it is biased. Just where the degree of skewness in the distribution balances the loss of precision due to the larger sampling error is a nice point and one not practically clear (a small bias may be permissible if a great gain in precision accompanies it). Consequently it is not possible to choose flatly between the two methods at present; perhaps the most

rewarding approach to skewed distributions ultimately may be to use transformations (e.g. log weight or index weight $^{0\cdot8}$ instead of weight) which will turn them into Gaussian ones, but at present too little is known about most anthropometric distributions for this to be practicable. An equivalent and practically simpler approach would be to tabulate the standard deviations and values corresponding, in the various skewed anthropometric distributions, to the first, fifth, 50th, 95th and 99th percentiles.

Distance versus Velocity Standards

We have now discussed what we mean by abnormal, and how we judge whether a given child reaches or does not reach our arbitrary limits of normality. We must next consider what sort of standards exist for judging children, and what advantages and disadvantages each possesses. Let us take first the measurement of one single dimension only, such as stature. There are four questions we may ask about a given child M. A. Is M abnormally tall or short at a particular age, say 6? B. Did M grow abnormally fast or slowly during a particular period, say 5 to 6? C. Was M's deceleration from the period 5 to 6 years to the period 6 to 7 years abnormally large or small? D. Was M's curve of growth in stature abnormal in any respect from birth to age 7 or to adulthood?

Growth is a form of motion, and question A seeks to characterize the motion by the distance achieved in a certain time, B by the velocity over a certain period, C by acceleration and D by a more complex consideration of the whole curve of motion from birth onwards. Question D is the most searching, but we may dismiss it at once, for it will be many decades before any acceptable standards for individual birth-to-maturity curves are available. Question C is almost equally impracticable at present and we are left with a choice between distance and velocity standards, answering questions A and B respectively.

Velocity Standards. Which question is the most rewarding to answer varies somewhat with circumstances, but other things being equal, it seems to me likely that the testing of velocity, or increments of growth, is to be preferred. Pathogenic factors would usually affect rate of growth directly and distance achieved only after the altered rate has had time to produce its result, so that one would expect earlier diagnoses of abnormality to be made by reference to rate. In this opinion also I am in the best possible company, for Shuttleworth has advocated using increments since 1934. All the same, velocity standards have never been seriously used up to the present and indeed very few usable standards exist. The reason for this appears to be threefold. First, the consultant paediatrician may only see a child once and, it is said, may never know anything about the child's increment. This is an argument which carries no weight in relation to the school medical officer and the general practitioner who have or could often obtain measurement records extending over several years, and for these to be made available to the consultant is a not insoluble administrative problem. Second, the determination of annual increment involves two measuring errors instead of one, and records are usable only if the measurements are made with reasonable care and accuracy and without looking at the card first to see what the previous figures were. Third, and by far the most important, velocity standards are extremely hard to come by, because they must give not only the average increments but also their variability, and to do this involves measuring children not just once but twice or more at yearly or shorter intervals. Velocity standards, in other words, must come from what students of child growth call longitudinal rather then cross-sectional growth studies, the former term referring to the measurement of the same children at different ages, the latter to the measurement of different children at different ages. Longitudinal studies carried over several years involve a good deal of money, administrative labour and the ability to wait a long time for results. Fleming's study (1933), confined to stature and head measurements, is the only one so far carried to the stage of publication in this country, though three studies are in progress at present, one at the Institute of Social Medicine at Oxford, another at the National Children's Home, Harpenden, under the joint sponsorship of the Ministry of Health and the Sherrington School of Physiology of St. Thomas's Hospital, London, and a third at the Institutes of Child Health and Education of London University. We are at present, therefore, dependent on the United States for this type of data: a short description of the major studies completed or in progress there will be found elsewhere (Tanner, 1949a), as well as a more extended one if required (Tanner, 1948). Even after the longitudinal study has been made there has been a further difficulty. Due to some children inevitably leaving in mid-course, the investigation always produces in the end a mixture of longitudinal and cross-sectional data, and there has been considerable confusion as to how proper velocity standards can be obtained from such records. Techniques have recently become available, however, as described previously (Tanner, 1951a).

There are four sets of data which seem useful for velocity standards. Robinow (1942) has given mean increments and standard deviations from birth to

age 6 for height and weight on approximately 100 children from upper middle class homes in Ohio; they were studied at the Fels Institute and the increments are reported in three-monthly periods to one year and six-monthly thereafter, the sexes being combined. Simmons and Todd (1938) have given yearly increments with standard deviations for height and weight from 3 months to 13 years, with the sexes separate. The annual increments are based on numbers which vary from about 50 to 150 of each sex for the various incremental periods, and the children are also mostly from upper middle class homes in Ohio. Palmer and his associates (Palmer and Reed, 1935; Palmer, Kawakami and Reed, 1937) have published annual increment figures for height and weight from age 6 to 14 for boys and girls separately, the data coming from the U.S. Public Health Service Survey of Hagerstown in Maryland, 1922-28. The numbers in this study are larger, ranging from about 200 to about 800 yearly, and all social classes are included. The standard deviations of the increments are given, but not the form of the frequency distributions. Probably this study is rather too old to be used as a standard nowadays; there has been considerable increase in the size of children at all ages during this century and data before about 1930 are to be avoided if possible: indeed the increase is still going on and the more recent the standardizing series the better. Lastly, Meredith and Meredith (1950) have published from the Iowa Child Welfare Research Station velocity standards for annual increments from 4 to 8, the data being obtained from approximately 200 healthy children of north-west European ancestry and coming mostly from the professional and managerial class. The 10th, 30th, 70th and 90th percentiles are given for weight, stature, sitting height, arm length, leg length, shoulder width, hip width, and chest, upper arm and calf circumferences. The sexes are combined, there being no significant differences over this age range.

Available Distance Standards

Height and Weight. There are considerable numbers of distance standards available for height and weight, and a few which include additional measurements. These standards are obtained from cross-sectional studies, or from mixed longitudinal studies treated as though they were cross-sectional. The best height and weight standards available for English (and probably Scottish and Welsh) use at present are probably those of Gore and Palmer (1949) for age 0-5 years and Daley (1950) for age 6-17.

Gore and Palmer report on a cross-sectional sample made in 1947 of children in London infant welfare centres; 5,684 children were weighed but unfortunately only 921 had their length (or height) measured. Mean weights and standard deviations are given weekly to 4 months, monthly to 1 year and three-monthly thereafter. Boys and girls are reported separately, and each mean is based on between 80 and 200 children. The main criticism of this standard is that no frequency distribution of weights are given, and no percentiles, so that one must use the standard deviation method without actually knowing whether this is justified, and with weight the initial assumption must be that it is not. Gore and Palmer's height data are much scantier; means and standard deviations are given for six-monthly periods from 1 to 5 years, but some of the figures are based on less than 30 subjects. Also the technique of measurement is not given, and this is a rather crucial matter in measuring the length of small children.

There are at present two possible sources of standards for the 5-17 age groups. Daley (1950) has reported the height and weight measurements taken in 1949 on 21,000 London school children and gives the means, standard deviations, 10th, 50th and 90th percentiles and the complete frequency distributions for each year, girls and boys separately. The 1st, 5th, 95th and 99th percentiles can thus be easily computed for the weight distributions, which are all skewed. Two objections can perhaps be laid against these figures; first that London children may not be a very good sample of all children throughout the country, and second that these children were weighed in their usual indoor clothes and by many different measurers and this always introduces inaccuracies and leads to standard deviations somewhat larger than they should really be. The weights reported include clothing (Daley, personal communication); to obtain nude weight probably about 7% should be subtracted. The first objection is probably not of much importance, since even if some small difference in mean weight and height exists between London and elsewhere this can be offset by using slightly altered percentile limits, as long as the scatter of the data in both places is similar.

MEASUREMENT TECHNIQUE. The second objection is more serious. It must be emphasized quite clearly that all anthropometric measurements, including height and weight, need considerable care and effort in the taking, and unless done properly are not merely useless, but confusing. It is not sufficient to let an unskilled person measure height without detailed previous instruction, and it is not sufficient to weigh children now in one set of clothes and now in another. To take measurements properly demands very little more time and patience than to take them

in a slovenly fashion, and unless the measurer is willing to expend this little extra energy it is better to leave measurement alone. Krogman's (1950) handbook on the measurement and interpretation of height and weight should be consulted in this connexion, also the remarks of Baldwin (1924). Briefly, stature should be measured with the subject standing as erect as possible, with heels, shoulders and buttocks touching an upright wall, the head poised so that the subject looks straight forward (external auditory meatus and lower border of orbit in the same horizontal plane), the occiput either touching or not touching the wall according to length of the head, and the heels together. A scale carefully ruled on manila paper should be stuck to the wall at an appropriate level, and a wooden ◣-shaped block should be brought down with the bottom face on the top of the subject's head and the rear face held against the wall. The subject is told to make himself as tall as possible without lifting his heels from the ground, and this is assisted by having him take a deep breath. Variation due to time of day is eliminated as much as possible by this latter procedure. Platform height scales are generally inaccurate and get more so with use and should not, therefore, be used; Krogman found errors of up to an inch on a selection of them. Height should preferably be taken with bare feet and in any case without shoes. It is useless to measure height with shoes on and apply a correction for heel height, for the simple reason that the lumbar curve is altered by the heel of the shoe being there. Weight should be taken on a beam scale and in the nude wherever possible. If not in the nude, standard clothing must be worn; either a smock as used in x-ray departments or else drawers for boys and pants and a brassiere for older girls. The point is that the weight of the clothing must be the same for each child, and unless some standard arrangement is adopted it will not be the same (see Krogman's table of various weights of summer and winter clothes, etc.). Weights should be recorded as nude weights, the standard clothing weight being subtracted.

The technique for other anthropometric measurements need not be described here, as investigators usually seek the help of a standard text before plunging into these. But a word about the recording of age in standard tables may be said. Some tables have their label ' 6 years ' refer to all children from $5\frac{1}{2}$ to $6\frac{1}{2}$ ('age at nearest birthday'), others to age 6 to 7; the user should make sure which he is dealing with in any given case. Also the width of the age interval makes a difference in the actual constructing of the standards. As the means and usually also the standard deviations of most anthropometric measurements rise with increasing age, the scatter amongst a group of children covering a six-month range is somewhat greater than the scatter of a group all of whom are exactly the same age. In the actual use of standards, however, it would probably be best to compare the child to be tested against the scatter of children of exactly that child's age. It is consequently desirable for standards to be made using the smallest age ranges that the magnitude of the data allows; three-monthly groupings are to be preferred to six-monthly or yearly. Alternatively one could correct for the gradually increasing standard deviation, but this does not seem ever to have been done in practice. The same considerations apply to the form of the distributions; if the height distribution of children all exactly 6 years old is Gaussian then that of children 6-$6\frac{1}{2}$ years old will be slightly positively skewed and platykurtic; this difficulty reaches a climax at puberty.

Returning now to the main discussion, the second set of figures covering the 5-17 age range are those recently published by Sutcliffe and Canham (1950). These are based on a cross sectional sample of 17,000 children taken in 1947 and drawn in a more or less representative fashion from rural and urban areas over most of England. The 10th, 25th, 50th, 75th and 90th percentiles and the standard deviations are given for each year, for boys and girls separately. The curious feature of this data, however, is that the 10th and 90th percentiles for weight are symmetrical about the 50th percentile at all ages, which is contrary to practically all other published figures. It would seem that either these percentile points have been calculated on the assumption of a Gaussian distribution for weight, or else by some smoothing process. The ' indices ' tabulated at the end of the book are, it appears, calculated on the assumption of a Gaussian distribution for weight, and so it seems wise to avoid using them at least until more stringent tests of the weight-distributions are published. It is noticeable also that though the medians for both height and weight agree fairly well between Sutcliffe and Canham's figures and the London ones, the standard deviations of the former are considerably lower. This is partly because the age group marked, for example, 6 years, refers only to the three-month range 5·11/12, 6·0/12, 6·1/12, and partly because the standard deviations were calculated not from the raw data but from the percentiles, assuming a Gaussian distribution (Sutcliffe, personal communication). It seems, as between the two sets of standards, that the London ones are at the moment preferable, though a reworking of Sutcliffe and Canham's excellent data is very desirable.

Other Anthropometric Standards. Astonishing though it may appear, there are at present no British standards for any anthropometric characters other than height and weight; however, this deficiency will shortly be at least partly remedied, when the results of a Ministry of Health Survey made in 1945 under the direction of Dr. E. R. Bransby, are published: about 2,500 children, aged 5 to 18, were measured, and 20 measurements were taken including height, sitting height, arm length, shoulder and hip widths, chest, waist, upper arm, knee, wrist and ankle circumferences, subcutaneous tissue folds and weight.

The main American standards with which the English should be compared, are those of Vickers and Stuart (1943), Simmons (1944), Gray and Ayres (1931), O'Brien, Girshick and Hunt (1941), Stuart and Meredith (1946) and Meredith (1946). Vickers and Stuart's data comes from middle and lower social class Boston children, and list means, standard deviations, range, 10th, 25th, 50th, 75th and 90th percentiles six-monthly from birth to 10 years for boys and girls for height, sitting height (or crown-rump at early ages), hip and chest width, head and chest circumference and weight. Simmons gives for Ohio upper social class boys and girls from 3 months up to 17 years means and standard deviations for 25 measurements including height, sitting height, shoulder, chest and hip width, chest circumference, arm length, and head length, breadth and circumference. Gray and Ayres give the mean and standard deviations for ages 1 to 19 of private school children of middle and upper social class for 15 measurements, including height, sitting height, shoulder, chest and hip width, chest circumference and weight: their monograph is still one of the prime sources of information in this field.

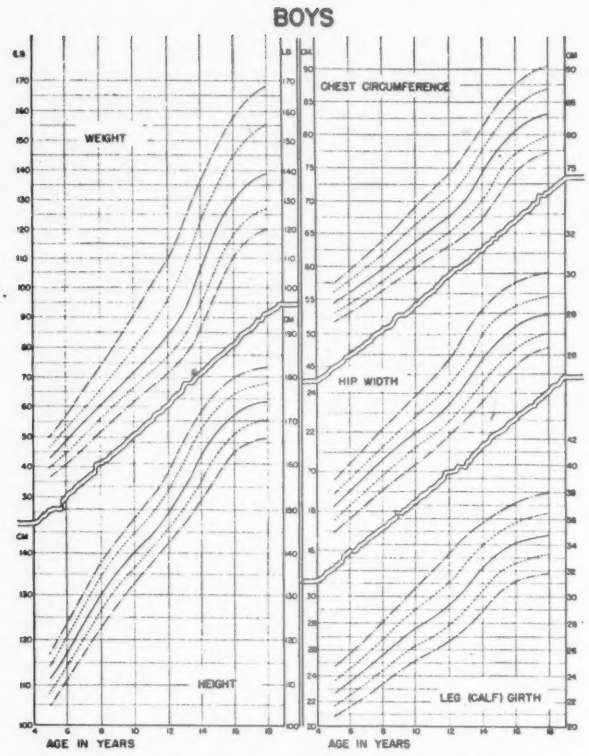
The U.S. Dept. of Agriculture survey reported by O'Brien, Girshick and Hunt comprises measurements on 147,000 children of all social classes, aged 4 to 17, and is the biggest survey of its kind yet made. Means and standard deviations for each year are given for 35 measurements, but most of these, being intended for use in tailoring design, are not those thought to be best suited for medical purposes; however, height, hip width, leg length, chest, upper arm, thigh and calf circumference and weight are given.

Stuart and Meredith's are perhaps the best contemporary American standards, and the paper in which they are introduced is certainly the best statement of the problems involved in supplying and using standards since Shuttleworth's note of 1934. Dealing with the selection of measurements they strongly deprecate reliance on height and weight alone and point out that the time required to take three or four more anthropometric measurements is only a couple of extra minutes or so, and the value of the examination is thereby enhanced out of proportion to the extra time spent.

> 'It must be remembered that height is only one aspect of size, and that the stockiness or linearity of skeletal build is only one factor in determining body weight. Furthermore, body weight does not differentiate between the amount of protoplasmic tissue and the amount of fat or water stored in these tissues; nor does it distinguish between relatively inert tissues such as bone, and active protoplasmic tissues, principally muscle. It is important to recognize that heavy weight for age may be due in one case to stocky bones, in another to exceedingly well-developed muscles, in a third to large accumulations of subcutaneous fat and in a fourth to a relatively well balanced amount of all these. When a change occurs in weight for age it is important to know which of these tissues has changed sufficiently to bring this about.'

In an endeavour to estimate the various tissues by simple means, Stuart and Meredith recommend five measurements in addition to height and weight, namely hip width and chest circumference (these two with stature giving a guide to linearity or ectomorphy), calf circumference (to measure muscular development) and subcutaneous tissue thickness under the scapula and above the crest of the ilium. Directions for taking the measurements are given in full except for the subcutaneous tissue folds which should be measured with the calipers designed for the purpose by Franzen (1929, frontispiece) and used extensively by nutritionists and constitutional anthropologists (Meredith and Stuart, 1947). Stuart and Meredith (1946) give percentile standards for boys and girls from 5 to 18 years; these are illustrated in Fig. 3, which is reproduced from their paper. Their tables give 10th, 25th, 50th, 75th and 90th percentiles at half-yearly intervals: the data are from Iowa school children of the professional and managerial classes measured between 1930 and 1945. These measurements and standards, it may be remarked, were deliberately published for the guidance of school medical officers in assessing children's health and growth progress. For an example of their use see Stuart and Kuhlman (1942).

These American distance standards are quoted here partly as examples in standard construction and partly because of the lack of British data. It does not seem likely that they could be used for British children without some modification of procedure, since American children, apparently of all social classes, are bigger, on average, than British. The difference in mean height is about 3 to 6 cm. from age 5 to 17, with the gap widening a little at the beginning of puberty, probably due to American children beginning their adolescent spurt slightly



From "Use of Body Measurements in the School Health Program" by Stuart and Meredith (1946).

FIG. 3.—Stuart and Meredith's percentile distance standards: the five lines in each graph represent the 90th, 75th, 50th, 25th and 10th percentiles. Iowa children of professional and managerial class.

earlier. The mean weight difference is about 3 lb. at the beginning of this age range and rises to about 10 lb. by the end. The standard deviations for height are about the same, but the American spread in weight is greater than the British at all ages.

Those interested in standards for more recondite measurements will find lengths of arm and leg bones by radiograph from 6 months to 12 years in Maresh (1943) and Andersen and Green (1948), and fat muscle and bone breadths of the calf as determined radiologically in Stuart and Sobel (1946), Lombard (1950), Reynolds (1948), and Reynolds and Grote (1948). Regression standards and standards for maturity are discussed below.

Use of Distance Standards for Assessing Velocity

Before considering more complex standards of the weight-for-height-for-age type, we must pause to illuminate, if we can, one particularly murky corner of this field. There are a considerable number of authors who endeavour to use distance standards for judging velocity. Two alternative ways of doing this are illustrated in Fig. 4. In Fig. 4A the child's height measurement is simply plotted from year to year in the typical percentile distance chart. Starting out at about the 80th percentile the child falls back to the 10th percentile between 5 and 7, and picks up again thereafter. The graph illustrates this well, but it takes us no further than simple illustration. The child in Fig. 4A never reaches our boundary of abnormality by reference to distance standards, even at age 7: common sense suggests that the increments from 5 to 6 or 6 to 7 are abnormally small, but Fig. 4A does not provide a test of this question; for this we need velocity standards with percentile charts of velocity from year to year.

The same is true of Fig. 4B, which is a rather more complicated way of dealing with the same data, but has some illustrative advantages. Here by developmental age is meant the age that the average child is when he reaches so many cm. of height: the same concept is used in constructing intelligence quotients and in making the skeletal ratings discussed below. Thus the average child progresses exactly up the diagonal line in Fig. 4B, with chronological and developmental ages always equal. The particular child we are considering, however, is in advance of average at age 2, then drops slightly behind in height, until at age 7 he is only the height of the average child of 6. This method has the disadvantage that usually neither distance nor velocity percentiles are shown; and having a 'height developmental' age a year less than chronological at age 4 implies considerably different conclusions from having the same difference at age 12, as may be seen by comparing percentile positions in 4A to developmental age advancement in 4B. Distance percentiles could be put in such a chart to remove this objection, but the trouble with velocity percentiles would remain. Admittedly 'developmental age' in several measurements can be plotted at once on this type of graph—we can put in weight developmental age, hip width developmental age and also skeletal and mental age—but the interpretation remains highly subjective. The best example of the use of this graph will be found in Wilkins' recent textbook (1950).

The method of Fig. 4A certainly has a great deal to commend it. Particularly when the record extends over several years the visual comparison of the subject's curve to the standard ones may be most illuminating. Also the situation may arise when a child suffers a succession of somewhat decreased velocities, none overstepping the limits of normality, but cumulatively producing an abnormally small child, as revealed, eventually, by the distance chart. It would seem perhaps best to use two percentile charts side by side in assessing growth in single measurements, one chart of distance and the other of velocity. Such a combined chart is given in

Fig. 5A, B, C, D. The data are those of the Brush Foundation from Simmons (1944) and Simmons and Todd (1938); standard deviations have been put in instead of percentiles because the data are only given in this form; percentiles would probably be preferable.

The two standards together enable one to assess both size and velocity and should therefore be more critical than any single-measurement standards using the same measurements now in use: only experience will show whether the expectation is borne out in practice. For more precise standards still one would have to use deviations from growth curves over several years; it might be sometimes practically important to do so, particularly in orthodontic work (see Count, 1942). A system of standards using distance and velocity data for single measurements and in addition, the relation of one measurement to another, is given below.

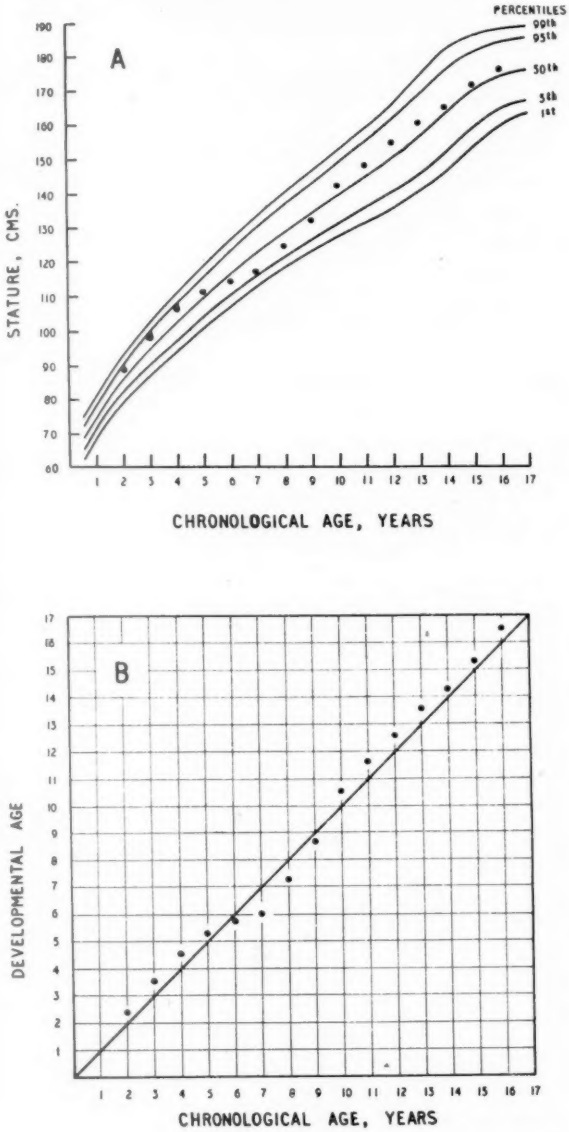


FIG. 4.—Growth of a hypothetical child with retardation from age 5 to 7. 4A. Plotted on the normal percentile type of distance standard. 4B. Plotted as chronological age versus developmental age. Note that neither method gives a test for abnormality of velocity.

Multiple Measurement Distance Standards

So far we have discussed only the use of single measurements for detecting abnormality. We have seen that a battery of such measurements, about seven in all, is the procedure recommended on biological grounds, but we have not discussed how the results of these seven measurements should be related together to give us an overall diagnosis. But if a child's scores on the seven measurements are six 75th percentiles and one 97th percentile, what are we to say? He is abnormal on one measurement, according to our single-measurement standards, but normal on six others. Again, if we had two children of the same age, one at the 95th percentile for height, weight and hip width and the other at the 95th percentile for height and hip width but the 5th percentile for weight, we would come to radically different opinions about the two; one is quite simply a large child, the other a child with a large skeleton and a probably abnormally small amount of muscle or fat or both. Clearly the relationships between two or more measurements give us added information about the child, information that we have so far neglected.

The complexity introduced into the situation as soon as we take two measurements instead of one seems not to be widely realized; with the second measurement we are well into the statistical jungle, populated only by a few semi-domesticated mathematicians and an occasional exotic psychologist. The trouble comes about this way: if we agree to call abnormal all children falling below the fifth percentile in height or in weight, then the number of normals called abnormal will no longer be five in 100, but more. Out of every 100 normals we shall ' reject ' (used from hereon to signify ' call abnormal ') five on the basis of height and five on the basis of weight. If height and weight bore no relation to each other our total rejection would be $5+5=10$, but since they are related some of our height-rejected children will be the same individuals as the weight-rejected, and the total rejected will be somewhere between five and 10. If we use height and weight in this way, in other words, we have altered our definition of ' abnormal ', for we defined it in the single-measurement case so as to reject just 5% of normals (or other fixed percentage).

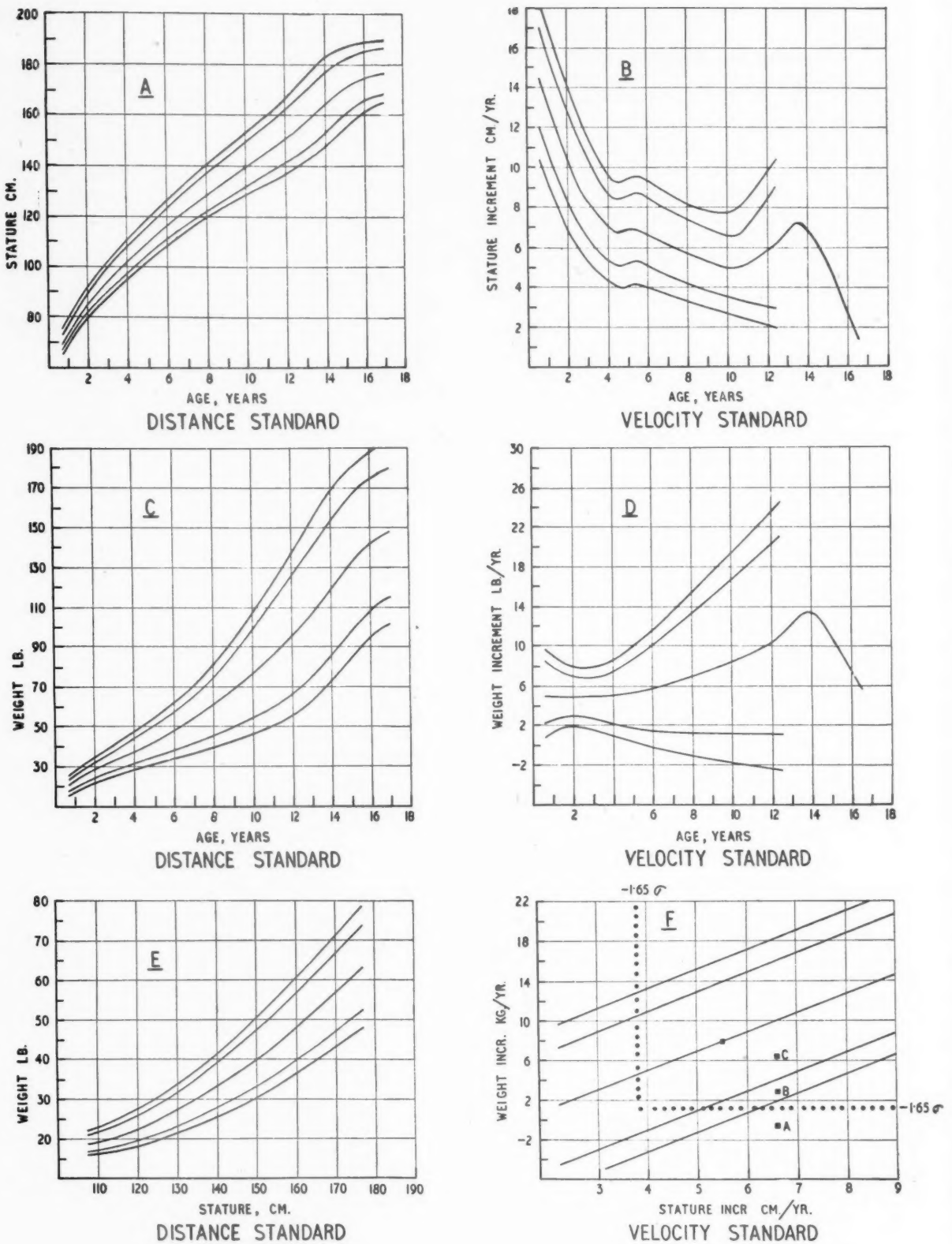


FIG. 5.—To illustrate suggested form for standards using two measurements only: a combination of distance velocity and regression data. Data in A, B, C, D and F are from Simmons (1944) and Simmons and Todd (1938) on Brush Foundation boys; for E from Daley (1950) for London County Council boys aged 5 to 16. The $\pm$ 1·65 σ and $\pm$ 2·3 σ lines correspond to the 5th, 95th and 1st, 99th percentiles in A and B; in C, D and E probably about the 2nd, 93rd and 1/10th, 97th percentiles: in F uncertain.

It will be seen that Stuart and Meredith's standards, amongst others, are subject to this uncertainty in interpretation.

Construction of Standards. We can meet this situation only by arranging our consideration of the two or more measurements so that in the end only 5% of normals are rejected by our total procedure, whatever it is. We have to combine height and weight somehow. This is very simple to do; we can use a thousand combinations: height/weight, height/$\sqrt[2]{\text{weight}}$, height/$\sqrt[3]{\text{weight}}$, height/log. weight, log. height − log. weight, height$^{\alpha}$, weight$^{\beta}$, anything. For each we can find a figure such that 5% of normals are rejected. But the various combinations will differ in the number of abnormals picked out for that 5% normal rejection; some will be powerful enough to pick out most of the abnormals, others will detect very few and hence have little practical value. It is in choosing our combination, that is in deciding the relative stress to be laid on height, weight, subcutaneous fat and so on in diagnosing abnormality, that we find ourselves statistically pathless, except in one set of circumstances, which we had better describe before going further.

When the characteristics of the abnormal, unhealthy population are known, besides those of the normal population, then we are in no doubt as to the correct procedure. In this case, we can calculate a line so that it separates, on the basis of two or more measurements, the abnormals from the normals with 5% (or any other chosen figure) normals rejected and the minimum percentage of abnormals undetected. Those above the line are normal, those below abnormal, only 5% of normals are misclassified, and our objective is achieved. The line is called a discriminant function. If the scatter of normal and abnormal populations is the same for, for example, height and weight, and the correlation of height and weight is the same in both populations, the line is a straight one, but if the scatters or correlations are different, as is much more likely in practice, the line is curved, an equation of the second degree (Smith, 1947). Not having any data available on groups of known well-nourished and ill-nourished children to take as an example, we must be content with an illustration from data previously reported (Tanner, 1951b). This is a situation in which we are trying, a trifle foolishly, to discriminate men from women (normals from abnormals) by shoulder and hip widths: if we have two measurements, biacromial and bi-iliac, the line which best discriminates is the one marked ' overall ' in Fig. 6A; its equation is

$$3 \text{ biacromial diam.} - \text{bi-iliac diam.} - 82 = 0$$

and it misclassifies the minimum number of men plus women. Parallel to this line we can draw others, misclassifying 5% of the men only or 1% of the men, as shown. The 5% line, the one we particularly want, is approximately

$$3 \text{ biacromial diam.} - \text{bi-iliac diam.} - 81 = 0$$

In short, we have calculated a combination of two measurements which, if more than 81, indicates normality, and if less than 81, abnormality. The combination we have calculated is the best combination; that is, it detects the largest possible number of abnormals for 5% normals rejected. One can try to distinguish men from women by the use of the ratio hip width/shoulder width, for example, but for 5% of men misclassified, a much greater number of women remain undetected among the men than by using the discriminant function line. The use of the discriminant can be extended to any number of measurements; in the example given the equation

$$2 \text{ biacromial diam.} + 0{\cdot}53 \text{ subischial (leg) length} - 1{\cdot}25 \text{ bi-iliac diam.} - 81 = 0$$

discriminates better than the two-measurement equation above.

In practice there are great difficulties in setting up standards this way, desirable though they would be. To use them we must know the characteristics of both populations, and this we seldom do. If we wanted, therefore, to use these standards as a screen for malnutrition from the usual variety of causes —economic hardship, maternal inefficiency, family disorganization, psychological disorder of child or parents—we would have to have located children whom we knew were quite definitely malnourished, and this is not easy. Stuart (1948) has well said that the therapeutic test of giving the child a known adequate food intake in a holiday surrounding with known psychological stabilization is the only sure way of telling whether a child has suffered retardation of growth progress through malnutrition. If the screen is to include lack—or excess—of growth progress through other factors such as the various endocrine disorders, the abnormal population becomes yet more difficult to locate and handle; its distribution is likely to be skewed and perhaps multimodal.*

When we do not know the characteristics of the abnormal population, or when they are simply too complicated to handle, we are forced to choose some combination of the measurements, locate the fifth percentile level for our normal limit, and hope that we are picking out as many abnormals with it as possible. There are no statistical grounds to guide us, and if we choose one combination rather

* That is, having several peaks instead of one.

than another, it is on an empirical or intuitive basis that we do so. The combination can be chosen in a number of ways, three of which are illustrated in Fig. 6B, C and D.

In Fig. 6B we follow the straightforward idea of using $-1{\cdot}65\sigma$ for biacromial and $-1{\cdot}65\sigma$ for bi-iliac as lower limits of normality for the men, but since these lines would exclude from the unhatched area not 5% of men but more, the limits are set at $-2{\cdot}0\sigma$, which is the multiple of each standard deviation which does lead, empirically in this sample, to 5% misclassified. Here we are giving equal importance to both measurements in the diagnosis. Should we do the same if we had height and weight and were trying to discover if a child were malnourished? Most would say not; more importance would be given to weight, but how much more? Twice as much so that the lower weight limit is something like $1{\cdot}8\sigma$ and the lower height limit $2{\cdot}2\sigma$? Or three times as much?

Several alternative ideas, some used in practice, suggest themselves. Fig. 6C illustrates one. Here the regression* of one measurement on another is taken for males and the $-1{\cdot}65\sigma$ limit for the biacromial-predicted-from-bi-iliac diameter used as the separating line (marked $-1{\cdot}65\sigma_{\text{est}}$ in figure). Correnti (1948-49) has used an elliptical area with the regression line as the major axis, rather than the $-1{\cdot}65\sigma_{\text{est}}$ line parallel to the regression line; his arrangement has some advantages. Or some ratio, biacromial/bi-iliac diameter, weight/height, height/$\sqrt[3]{\text{weight}}$ and so on can be used. Lastly the methods of Fig. 6B and C can be combined as in Fig. 6D, which gives some importance to both absolute size of measurement and the relation of one measurement to another.

Regression standards have been widely used, and must be discussed at some length. They will probably be familiar to the reader, though perhaps not under this name. The weight-for-height-for-age tables are the commonest example, the best known being those due to Baldwin and Wood (1923; Baldwin, 1924, 1925) and to Faber (1929). In this type of standard the expected weight is given corresponding to the various possible heights, and this is done for each year of age separately. Suppose we have a boy aged 10 whose height is 140 cm. and weight 72·5 lb. Finding 10 years in the table, we look up the expected weight of 10-year-old boys of 140 cm. height and find it to be 78·5 lb. The boy is 6 lb. below the average weight for his height at this age. If the tables have been properly constructed, we should also find the percentile spread about the expected weight figure, or the standard deviation around the expected figure (the standard error of estimate, in the usual terminology of the regression equation). The Baldwin-Wood tables give only the mean expected figure, however, and Faber gives only the 10th and 90th percentiles. Let us suppose the standard deviation around the expected value is 9 lb.; the boy is then $6/9=0{\cdot}67$ standard deviations below the expected mean, and if we pretend for the moment that weight has a more or less Gaussian distribution for given height, then this corresponds to about the 25th percentile, which is not very far down the total list of boys. A regression standard (for increments this time) is shown graphically in Fig. 5F, the central line being the expected weight increment for height increment and the parallel lines the $\pm1{\cdot}65\sigma$ and $\pm2{\cdot}3\sigma$ limits for the estimate. (The data are from Simmons and Todd (1938) and a linear regression of weight increment on height increment and also homoscedasticity* has been assumed, perhaps unjustifiably, for illustrative purposes and because data on the point are lacking.) In Fig. 5F the lower $1{\cdot}65\sigma$ limits for weight increment and height increment have also been indicated. If we were judging by the regression standard, the child designated by B in the figure would be called abnormal; if we were judging by weight increment only, B would be normal, being just above the $1{\cdot}65\sigma$ level. Child C would be normal in either case, and child A abnormal, but if we used the technique shown in Fig. 6B, giving equal importance to both variables and rejecting 5% only, then even A would probably be judged normal, as the lower limit for weight would be somewhere about $1{\cdot}8$ to $2{\cdot}0\sigma$.

This is merely repeating what is already shown in Fig. 6; in each drawing A, B, C, D, 5% of normals are rejected, but not the same individuals in each. In Fig. 6 we have the discriminant function line which we know is the best one and we can compare the other techniques with it. The regression method (6C) in this example comes out better than any set of horizontal and vertical boundaries drawn after the manner of 6B; it detects only two fewer abnormals than the discriminant. Whether regression standards are preferable to standards of the 6B type in all or even most circumstances in child growth is not known at present. The efficiency of any regression depends first on the correlation

* If we have two measurements x and y we can relate them by means of a line which predicts the most likely value Y for any given value of X. This line

$$Y=a+bX$$

where a and b are constants, is called a regression line. Unless the measurements are perfectly correlated one with another the prediction of Y from a value of X is subject to a certain amount of error; most of the points do not actually lie quite on the line, but round about it. The amount of this error in prediction is measured by the statistic σ_{est}, the standard error of estimate. Its interpretation is that of all the values actually obtained for Y at a given value of X about 95% lie within the range $\pm2\,\sigma_{\text{est}}$ from the predicted value of Y.

* Equality of variability in Y (weight) for each broad division of X (height).

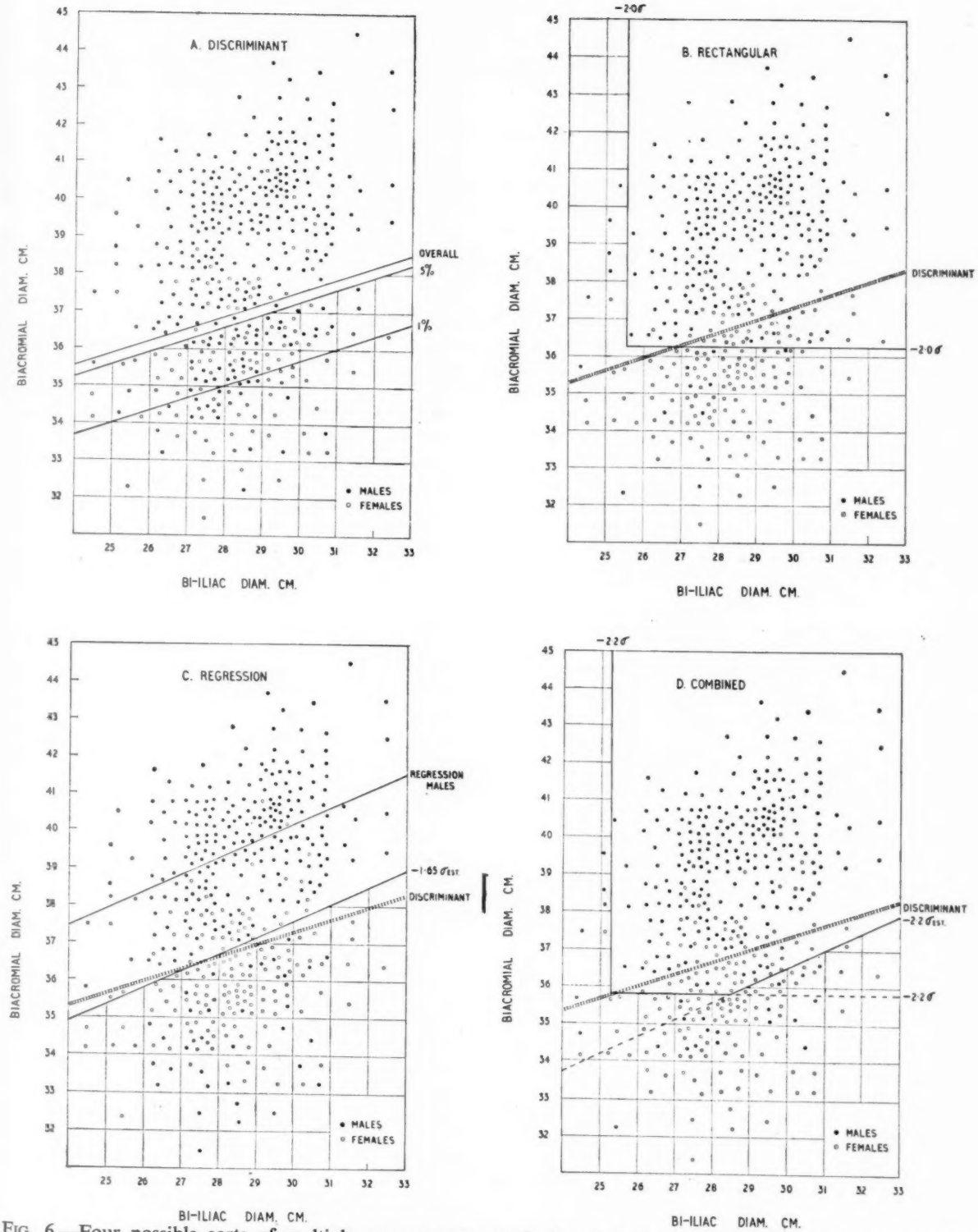


FIG. 6.—Four possible sorts of multiple measurement standards. In each case the hatched area represents the area of abnormality, defined so that 5% of normals are called abnormal. Males are taken as normals, females as abnormals. Fig. 6A. Discriminant lines, giving best separation of normals and abnormals. Fig. 6B. Equal importance given to both measurements singly; 25 fewer abnormals detected than by discriminant. Fig. 6C, regression standard; 2 fewer abnormals detected. Fig. 6D, combination of B and C; 31 fewer abnormals detected.

between the two measurements (since if there is no correlation the relating together of the two is simply an irrelevance), and second on the disease process, whatever it is, altering one measurement and not the other. If the disease causes both measurements to alter proportionately, then their relationship stays the same, and, if the child's point falls on the regression line to start with it merely moves up or down the regression line (see Fig. 6C) and not away from it. In such circumstances the technique of Fig. 6B would be better, for by this method the proportionate increase or decrease will be detected, the child moving from, say, a position of $-1{\cdot}0\sigma$ in both measurements to the abnormal position of $-2{\cdot}3\sigma$ in both.

The construction of regression standards is a simple matter. If two anthropometric measurements are adequately related by a straight line, and if the y-axis measurement is distributed in a Gaussian form for each broad division of the x-axis measure, then the expected value Y′ of any measurement for the value X of another measurement is

$$Y' = a + bX$$

where a and b are constants obtained for the standardizing data by simple statistical procedures; b is known as the regression coefficient. The standard deviation around this expected value Y′, σ_{est}, is also simply estimated, and if r is the correlation between the whole series of X and Y measurements at this age $\sigma_{est} = \sigma_y \sqrt{1-r^2}$ where σ_y is the standard deviation of all values of Y. (In this section and above I have assumed large samples and avoided discussing problems of estimation, not because they are unimportant, but because they would complicate the exposition intolerably.) The principle can be extended to more than two measurements; Y′ can be predicted from X, Z, A and B by, for example,

$$Y' = a + bX + cZ + dA + eB$$

with a σ_{est} of $\sigma_y \sqrt{1-R^2}$ where R is the multiple correlation of Y with X, Z, A and B. If the relationship of one measurement to another is not adequately represented by a straight line, but requires a curved one, the same principles still hold. The situation is then as illustrated in Fig. 5E; curved percentile lines run either side of the curved line of expected weight.

In using the regression standard one may calculate from the standard the expected weight, say, for the measured height, and then compare the difference between this and the actual weight with the figure for σ_{est}, as in the example above. For this procedure to be valid it must be emphasized that two conditions must be met. The distribution of weights for any given broad division of height must be Gaussian, and the standard deviation of the weights must be the same for all height divisions (i.e. normality and homoscedasticity of weight arrays). If the former condition is not met then percentiles must be used, and if the latter is not met, then different standard deviations or percentiles must be used for each division of height, a laborious business. These considerations apply whether the regression line is straight or curved, rectilinearity being a separate issue. Since in general one cannot find transformations which simultaneously reduce the relation to one of rectilinearity, homoscedasticity and normality of array distributions, it is necessary to decide which reduction is the most important. This would seem to be the production of a Gaussian distribution in the arrays, with homoscedasticity of arrays as the next desideratum. Rectilinearity comes last. Some standards have been proposed—for example, the Wetzel grid discussed below—in which rectilinearity has been achieved over considerable ranges, but at the expense of non-Gaussian array distributions. Though such standards can be used with percentiles instead of standard deviations, their construction does not seem a very appropriate one.

Regression standards in current use are divisible into two classes; those which operate over a restricted age group, which we will call 'within-age regression standards', and those which operate quite without reference to age at all, which we will call 'irrespective-of-age regression standards.' Fig. 5F is an example of the former, and Fig. 5E of the latter. In Fig. 5F the standard holds only for the age range 9-10 years, and is one of a set of similar regressions, one for each year of age. The Baldwin-Wood and Faber tables are regressions of this sort. But instead of this we can ignore age and simply use a weight-for-height regression covering the whole period of growth, as in Fig. 5E.

It is essential to have clear the difference between these alternatives. In the first case, we test the child M on the basis of weight-for-height at his age, and place him in relation to the expected mean and standard deviation for boys of his chronological age. In the second, we test M on the basis of weight-for-height at his height and place him in relation to the expected mean and standard deviation for boys of his height. Thus, if we have a boy aged 10 who is advanced for his age both in height and weight, the first method will predict his expected weight by a regression coefficient appropriate to 10-year-olds, and compare his deviation from the expected value with the σ_{est} for 10-year-olds. However, the boy may perhaps be better regarded as nearer the average 11-year-old state, since he is about an 11-year size, and the regression coefficient for

11-year-olds is larger than that for 10. The expected value would therefore be somewhat different, and so the deviation would be different. Also the σ_{est} would probably be larger at 11 than at 10, and the result of the test pretending the boy was 11 would be different from that made keeping him at 10. Only in one circumstance will this not be true; if the expected weights for both year groups are the same, and the deviations from expected weights in each of the groups are proportional to the standard deviations of the groups, then the test result will be the same whichever group the boy is tested in. (This is now on the assumption that we are using a transformation of weight which brings it to a Gaussian distribution.) For the expected weights to be the same the regressions must be the same for both age groups and the coefficient must be equal to the average weight gain from 10 to 11 divided by the average height gain: for the second condition above to be satisfied we must have the same height-weight correlation at both 10 and 11. When these conditions are met for all age groups then there is no difference between the two alternative regression methods. If the condition of equal correlations at all ages is met, as it is fairly closely at least up to the last two or three years of growth (Tanner, 1951a), then the conditions reduce to mean yearly gain in weight/mean yearly gain in height being constant, and equal to standard deviation of weight/standard deviation of height, the latter ratio being the same for all age groups. These conditions are not met by weight and height in their usual measurement scales, but they are met by using standard scores as described below.

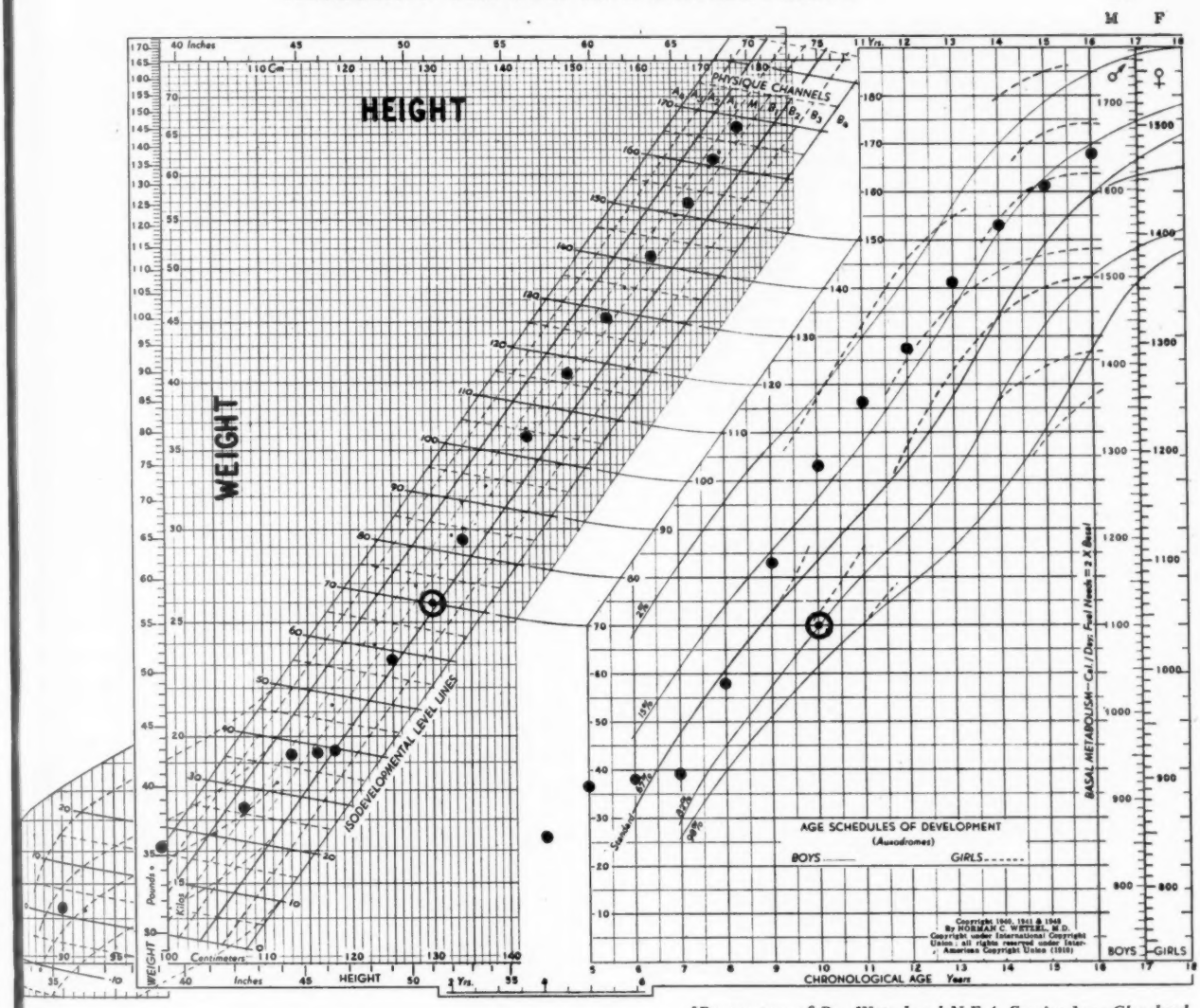
Considerable numbers of distance regression standards have been suggested, most of them of the within-age variety, which have the advantage of being nearer rectilinearity for most combinations of measurements than irrespective-of-age regressions. Most of these standards aim at predicting body weight from various skeletal and/or muscular measurements. Pryor's (1936, 1941) tables predicting weight from height and hip width are of the best known and are given in Holt and McIntosh's textbook (1940). The idea is that the two skeletal measurements give a fair idea of skeletal size and build, and then weight ought to follow accordingly, but weight in fat and weight in muscle are not, of course, distinguished. The most thorough studies of weight prediction by various combinations of measurements are those of Franzen (1929), McCloy (1936, 1938) and Dearborn and Rothney (1938). The first of these accounts in particular deserves to be better known than it is at present; it covers with clarity and distinction a great deal of the ground surveyed in this paper. Franzen discussed the prediction of weight from four skeletal measurements, but suggested that for nutritional purposes weight prediction standards are not as good as prediction of upper arm girth, calf girth and subcutaneous tissue thickness over the biceps. The former two are predicted from height, chest breadth, chest depth and hip width, and subcutaneous tissue is predicted from height, chest breadth, chest depth and shoulder width. Franzen's regression standards were tested in the field by Mitchell (1932) who used them successfully to pick out malnutrition in Porto Rican children and relate this to such factors as family income and overcrowding. Mitchell's paper also seems to be less well known than it deserves. Massler and Suher (1951) have recommended a ratio type of standard, weight being predicted by (calf circumference)$^2\times$ stature divided by a constant, which is independent of age over the range 5 to 17. No percentile limits or tests of distribution are given.

The Wetzel Grid. A consideration of the Wetzel grid (1941, 1943, 1944) standard falls due at this juncture. Armed with the discussion above, courage, a magnifying glass and steady nerves, the reader will be able to make out that the grid, reproduced in Fig. 7, is in essentials simply a weight-for-height regression distance standard, presented with a recommendation to use it as a velocity one. The regression standard is neatly combined with a distance-for-age standard, and is of the irrespective-of-age type, with a logarithmic transformation of both weight and height used to get the regression from the curve of Fig. 5E above to a straight line, at least from age 6 onwards. Look first at the left hand portion of Fig. 7; the graph is one of log weight vertically against log height horizontally. Consider a child M of height 130 cm. and weight 26 kg.; locate the point, ringed in the figure, which corresponds to these figures. Look at the 'physique channel' lines running north-eastward, and it will be seen that M lies in channel B1, near the B1-B2 boundary. Since the middle channel corresponds to the average child, this B1 position tells us that M weighs a bit less than the average child of his height. If we go up to the 130 cm. vertical line till we get to the middle of the centre channel M we find the weight of the average child of this height is actually 28 kg. This information, then, is the same as that given by a weight-for-height distance regression except that it is less precise, since no standard deviation σ_{est} about the mean expected weight is given. We cannot judge how far down amongst his height group a weight of 2 kg. below average brings M. That it brings him to the B1-B2 border does not of itself tell us what we really want to know, which is his

percentile position. The channels may be actually misleading in this regard to the unwary; from their graphic presentation as of equal width one might readily assume that the distribution of log weight for log height was Gaussian and homoscedastic about the mean of channel M. Whether or not this is so still cannot be discovered from the published studies; Hopkins (1947) gives a graph of log weight against log height for girls aged 6-12, and in this it looks as if log weight is still skewed, particularly for the larger girls. For a given size (that is auxodrome 100, see below) the distribution of log weight is certainly heavily skewed with an excess of cases in the B channels below the mean (Wetzel, 1941), so that being in channel B2 at what almost amounts to a given log height implies a percentile position considerably nearer the 50th than does being in A2. Also one must remember that though these lines are called 'physique channels', M's position in them really tells us very little indeed about his physique in the true sense. It takes a great deal more than simple weight for height to characterize a human body, in which connexion the remarks of Stuart and Meredith quoted above are pertinent.

Now consider the line passing in an east-south-east direction through M's position on the grid. It is called 'isodevelopmental level' and marked 70. Follow it down to the right hand portion of the chart and consider this portion. It is seen to be simply a percentile chart of growth with age, the same as those in Figs. 3 and 4A and 4C, except that the vertical scale is neither height nor weight, but a composite of the two. If, for example, M was 130 cm. tall but weighed 29 kg. instead of 26 kg., his level on the right hand chart would be 80; if his weight were 26 kg. but his height 120 cm. instead of 130 cm., his level would be about 67. A change in weight of 3 kg. is not a great deal, yet it produces a far greater effect on isodevelopmental level than a change of 10 cm. of height, which is quite a lot. The composite measurement is of the same nature as surface area, also obtained from a combination of weight and height, but it gives much greater emphasis to weight as opposed to height than does the DuBois expression for surface area. The idea of using a composite of the two measurements to measure size for age is undoubtedly a good one, but this particular composite is probably not the best available. Presumably what is theoretically required is something approximating the general size factor for body build, and at least in adults, as I have pointed out elsewhere (Tanner, 1949c), this is very closely approximated by the DuBois surface area. Returning now to M, we disclose his actual age as 10 years, say. Follow the 70 line to the right till it meets the vertical 10 year line at the ringed point. A percentile line goes through this point; M lies on the '82nd percentile' of size for age. This is approximately the same information as is obtained by reference to Meredith and Stuart's curves of Fig. 3, or those of Figs. 4A, 5A and C; it is not quite so full, however, in that it gives only a somewhat questionable 'size' rating instead of separate height and weight ratings. Note also that Wetzel gives his percentiles in the opposite sense to those in Figs. 3 and 5, marking the children from the bottom up, so to speak. In addition, the middle of the percentile lines given in Wetzel's chart is not, as one might expect, the 50th percentile, but the 67th, or in the more usual terminology, the 33rd. A 'size developmental age' is given by reference either to this 67th percentile or, by some later authors, to a 50th percentile precisely as for the height age graphed in Fig. 4B; the size developmental age is the age at which the 67th (or 50th) percentile crosses the horizontal line reached by the child, in the case of M $8\frac{3}{4}$ years for the 67th percentile, about $8\frac{1}{2}$ years for the 50th.

Wetzel now recommends this procedure to be followed for M every year, when a series of points will be produced on both left and right hand portions of the chart. These, plotted in solid dots, are for the same hypothetical child who gave the points in Fig. 4A and B. The dots on the right hand portion are precisely similar to those in Fig. 4A except that Wetzel's measure of size is plotted instead of height. From the point of view of interpretation the situation is just the same as in Fig. 4A; graphically the drop in velocity between 5 and 7 years is shown quite well, but no tests of whether the drop is abnormally large or not can be made. We are again using a distance standard for judging velocity. The dots on the left hand chart require a little more analysis. Wetzel assumes, it seems from *a priori* consideration, that from about 6 years onwards a healthy individual travels a straight course up one of the channels, in other words, maintains a constant ratio of log height:log weight. This is certainly true of the mean values of such data as of the Brush Foundation (Simmons, 1944) and is very nearly true for the mean values of the London County Council data (Daly, 1950). If a child slips out of his channel in a southerly direction, as does the one illustrated in Fig. 7, then he is said to be gaining too little weight for his gain in height, and if he deviates to the north he is said to be gaining too much weight for his height. Again, the method is very aptly illustrative, and by using logarithms Wetzel has obtained a straight line regression for weight on height over a fairly large age range, which is certainly desirable, though not at the expense of producing



[*By courtesy of Dr. Wetzel and N.E.A. Service Inc., Cleveland.*

FIG. 7.—Wetzel grid. The solid dots represent the growth of the same child as illustrated in Fig. 4A and B.

skewed or heteroscedastic weight arrays; and whether or not these are produced we do not know. But again it suffers from the disability of distance standards used as though they were velocity ones. Over the straight line portion the standard lays down that increment log weight=k. increment log height, a velocity regression of a similar nature to Fig. 4E. But no figure for σ_{est} is given, and no data as to the distribution of increments of log weight for given increments of log height; weight increments are usually somewhat positively skewed, but one's suspicion is that taking logarithms may overcorrect. An apparently empirical tolerance limit of $\frac{1}{2}$ channel deviation in 10 isodevelopmental levels is mentioned, but its source is not clear and it assumes quite uncritically homoscedasticity of arrays from age 6 on and, presumably, since deviations in either direction are subject to the same rule, a Gaussian distribution in arrays. What has been said above about any regression standard for weight on height not necessarily distinguishing abnormals if the disturbing influence affects both measurements proportionately applies, of course, also to the grid. Apart from these points, however, the grid does seem a neat way of recording weight, height and weight-for-height data so long as the user understands clearly its simplicity of approach and the limitations to the information it gives. Various tests of its use in practice have been made and various opinions passed (Bruch, 1942; Simmons and Greulich, 1943; Stuart and Meredith, 1946; Dreizen, Mann and Spies, 1948; Mann, Dreizen, Pyle, and Spies, 1948;

Krogman, 1950). It does seem to me that the grid has little or no advantage over percentile graphs for height and weight combined with a weight-on-height regression standard, and it cannot compare in usefulness and accuracy with the simultaneous use of distance and velocity charts as outlined in Fig. 5 and discussed in the following section.

Other Standards. Correnti (1948-49) has recently published a weight-for-height auxogram, which has a much firmer biometrical foundation than the Wetzel grid, and seems in many respects preferable to it. The auxogram is a height-on-weight regression, the variables untransformed, the regression therefore curvilinear. At each year of age the means of height and weight are plotted, and around them an ellipse, containing some particular percentage (say 90%) of the total children of that age. Those within the ellipses are normal, those without are not. The ellipses are calculated on the assumption of a joint Gaussian distribution of height and weight for each age, and this is certainly a questionable assumption. Also the auxogram is subject to the criticism of distance standards being used for judging velocity.

TUXFORD'S INDEX. Another distance standard recommended for use as a velocity one is Tuxford's (1939, 1942) index (Campbell and Weir, 1948). Tuxford uses the ratio weight/height rather than a regression equation for comparing the two measurements, and his method essentially gives simply the mean weight/height at each age from 5 to 16 for boys and girls. He found, however, that this ratio decreases approximately in a straight line with increasing age, so that instead of giving a distance table for weight/height at each age, a linear correction for age brings back the mean weight/height to very nearly 1·00. Tuxford's index (1942 edition) is founded on the 1938 London County Council data given by Menzies (1940), and for boys is

$$\text{T.I.} = \frac{\text{Wt. (kg.)}}{\text{Ht. (cm.)}} \times \frac{335\text{—age in months}}{48}$$

and for girls

$$\text{T.I.} = \frac{\text{Wt. (kg.)}}{\text{Ht. (cm.)}} \times \frac{308\text{—age in months}}{42}$$

The mean of the index is not exactly 1·00 for each age in these data, but comes fairly close to it except for boys at age 14 where T.I.=0·987, and for girls aged 5. No standard deviation or percentile spread at any age is given, so that even as a distance standard the index is impressionistic only. Tuxford says that values below 0·95 deserve investigation, but the basis of this statement is not clear, and it seems to assume that the scatter of weight/height is the same at each age, which certainly cannot be the case. If a value of 0·95 is a warning at adolescence, then something much nearer unity should be the warning at, say, 6 years. Even if we had percentile limits, however, one would still be somewhat uncertain how precisely to interpret an abnormal ratio: ratios may look simple but they are biometrically a bit complicated and present to the statistically unsophisticated several pitfalls, some of which I have discussed elsewhere (Tanner, 1949b).

Tuxford also recommends using his index to judge velocity, and this in very much the same way as the channel system in Wetzel's grid. In health the Tuxford index is assumed to be constant from year to year, this being the equivalent of straight progression up the channel. This time the standard is weight/height increment = −c. age increment, but again no figure for σ_{est} is given and no data as to the distribution of weight/height increments for given age increments. Tuxford suggests that a change of index of 0·02 over a year should be regarded with suspicion, but whether this applies equally at all ages is not clear. It is interesting to compare the use of Tuxford's index and the Wetzel grid in one of the articles (Wetzel, 1942) in which Wetzel first fully introduced his system. Wetzel criticizes the Tuxford index and alleges that it does not show that the particular boy used as an example is retarded in growth progress, whereas the grid does. Unfortunately for his thesis, however, Wetzel uses Tuxford's index quite wrongly, applying the empirical distance criterion where he should apply the velocity one; used properly the index shows the falling weight-for-height at exactly the same time and with the same force as does Wetzel's channel system. Neither, however, can be considered very satisfactory.

Velocity Regression Standard. There have so far been very few attempts to construct a proper velocity regression standard of the sort shown in Fig. 5F. Bransby (1945) has suggested and tentatively used a standard for weight attained after so many years at school for height increment during residence at the school. Further subdivisions were made by age at entry to school and weight at entry. Thus a standard curve of weight attained for given height increment was provided for each 2 lb. weight group and each year of age at school entry. In other words, the 10-year-old 62 lb. child had a standard curve covering the rest of his school career, the 10-year-old 64 lb. child another, and the 11-year-old 64 lb. child a third. The material was insufficient for percentile limits to be accurately laid down, but the approach is an interesting one and might repay more extensive study. This method combines velocity in one measurement with distance in another, a perfectly simple and useful possibility

in regression standards. Also two values of the same anthropometric measurement at different ages can be used if desired; for example, in constructing a standard for weight at age 1 or 2 or more by regression on birth weight (Asher, 1950; Illingworth, 1950) or in comparing the growth of children of different economic groups (Greenberg and Bryan, 1951). Bransby and Hammond (1950) are currently considering whether standards of this general sort for subcutaneous tissue change over fairly short periods would have screening value for the assessment of malnutrition. Stuart and Reed (1951) have dealt with the same problem by fitting straight lines for each individual to the growth in volume of subcutaneous tissue by radiograph of the calf over the age range 1 to 6 years: the fit is good but the residual variance about the line is significant, which is not the case for muscle and bone lines. The causes of a significant departure from the line are then sought. This method begins to approach a test of hypothesis, D above (page 14), of growth being normal over a whole range of years, and may turn out to be a most powerful technique.

Suggested Form for Combined Distance, Velocity and Standard-score Difference Standards

It is possible that a small simplification of the regression type of standards could be made along lines rather vaguely suggested elsewhere (Tanner, 1950, 1951a) and if this simplification is combined with both velocity and distance standards an overall test for abnormality more adequate than any so far available might perhaps be achieved. The use of the distance and velocity standards as suggested in Fig. 5A, B, C, D, implies finding first of all the standard deviation score or percentile for the two measurements, let us say height and weight, and it is easy to see that the difference between these scores for the two measurements relates height and weight to one another in the same sort of way as does the regression equation. If X cm. is the height of a child age 6 say, $\overline{x}$ cm. the average height of 6-year-olds, and σ_x the standard deviation of 6-year-olds, then the score $z=\frac{X-\overline{x}}{\sigma_x}$ is called the standard score for the child. All standard scores have a mean of zero and a standard deviation of unity. The mean difference of the two standard scores will be zero, and the standard deviation of this difference will be $\sqrt{2(1-r)}$, where r is the coefficient of correlation between the two variables concerned. Thus if a child has standard scores for height and weight of $+1\cdot2$ and $-0\cdot8$ respectively, his standard-score difference is

$$z_{wt}-z_{ht} = -0\cdot8-1\cdot2 = -2\cdot0$$

The test for whether such a difference could have arisen in a normal healthy population or whether it indicates that the child is abnormally underweight for height is made by comparing this height-difference with its standard deviation. If the correlation between height and weight at the age considered is $0\cdot75$, then the standard deviation of the height-weight difference is $\sqrt{2(1-\cdot75)}=0\cdot7$ units. The ratio of height-weight difference to its standard deviation is therefore $\frac{-2\cdot0}{0\cdot7}=-3\cdot0$, which is far out beyond even the first percentile (which it will be recalled is at $2\cdot3\sigma$) and undoubtedly signifies abnormally low weight for height.

This procedure seems to me rather simpler than the usual regression computation, and gives the same information. Admittedly the example above is badly chosen, in that the distribution of the Y variate should be Gaussian for each broad division of X, and these distributions should have the same standard deviation. However, it should not be too difficult to allow for skewness of weight arrays either by the use of tables transforming weight, as suggested in the footnote to Fig. 8, or by adjustment

GROWTH PROGRESS CHART

AGE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
MEASUREMENTS																	
HEIGHT																	
WEIGHT																	
⋮																	
HEIGHT INCR.																	
WEIGHT INCR.																	
⋮																	
STANDARD SCORES																	
HEIGHT																	
WEIGHT																	
⋮																	
WT. - HT.																	
⋮																	
HEIGHT INCR.																	
WEIGHT INCR.																	
⋮																	
WT. INCR. - HT. INCR.																	
⋮																	

FIG. 8.—Increment 1-2 years entered under 2 year column. Ring in black standard scores coming below 5th or above 95th percentile; in red scores coming below 1st or above 99th percentile.

The chart is accompanied by three tables:

A. Pearl's tables to convert increments to per year.
B. Tables for turning measurements to standard scores; incorporating transformation for non-normally distributed measurements.
C. Tables for percentiles corresponding to standard score differences for each pair of measurements at each age if necessary.

of the final value corresponding to the figure of −3·0 in the example above. If the within-age type of regression (see page 24 above) is wanted it would be necessary to give a table of correlation coefficients (or actually of $\sqrt{2(1-r)}$) for each pair of anthropometric dimensions at each year of age, and this is the preferable form if the regression is at all curvilinear. If the irrespective-of-age regression is required, then the standard scores are obtained by reference to the mean and standard deviation of the measurements at all ages, and the correlation is the overall correlation for the whole age range. However, one of the advantages of standards couched in this way is that when the regression is rectilinear, the conditions for the two types of regression tests to be identical, as outlined above on page 25, are met if the correlations at each age are the same. For the height-weight correlation the published figures show little trend during growth up to the last two or three years (Wilson, 1935; Simmons, 1944). It seems that a figure of about 0·75 would cover adequately both boys and girls, the former for age 1 or less to age 16, the latter from 1 or less to age 13. The correlation for weight increment-height increment is about 0·40 from 2 till 12 (Simmons and Todd, 1938).

The form of the report suggested is given in Fig. 8: the upper block contains the actual figures for weight and height and any other measurements taken, at each age, and the figures for their velocity. The 1 to 2 year velocity is placed in the 2-year-old column and all velocities are given as so much per year since the intervals between successive examinations are inevitably different on different occasions; for example, 360 days one time but 380 the next. Pearl's tables (1940) giving the proportion of a year lying between any two dates can be used to facilitate the conversion. The lower block in Fig. 8 contains the standard scores, obtained by reference to the standard tables used, that is tables embodying the lines of Fig. 5A, B, C, D. One new item appears here; this is weight−height, one standard score being subtracted from the other. Reference to a third table completes the job; in this are listed the percentile points corresponding to the standard scores and the standard score difference for each year, the table being constructed on the basis of the distribution of the standardizing data. If the correlations between two measurements are equal each year then this system is equivalent to either regression standard; if not, then it is equivalent to the within-age type only; but it could be extended to the irrespective-of-age type by reference to another table wherein standard scores for weights appropriate to various height groups were entered.

The construction of British standards of this sort would probably be immediately possible for height and weight. The distance data have been discussed above and though, so far I am aware, no means and percentiles for height or weight increments have yet been published in this country, several local authorities and secondary schools must have the data in their files. Pending their production, however, it might prove possible to use the American velocity data after a little experience had been gained in their interpretation, or to use, as a temporary expedient, British mean increments obtained cross-sectionally with percentile limits from the American data.

The interpretation of such standards is subject to the uncertainties discussed above, and it seems at present impossible to suggest anything more positive than caution in using multiple standard scores, or if this is impossible, reliance on one sole item such as weight increment standard score minus height increment standard score, or whichever is found to work best in practice.

Standards for Maturity

The advent of the adolescent spurt in growth bedevils all the standards so far discussed. The reason for this is that there is a wide spread between individuals in the time at which the spurt starts, and so, with some children suddenly speeding up tremendously and others not at all, the scatter of the normal increases greatly. Consequently our standards, though perfectly valid still, become far less potent for detecting abnormality. We need to combine them with some index of whether adolescence has started or not.

In longitudinal growth studies several ways have been used for indicating the relation of a child at any time to his adolescent spurt. For girls menarcheal age is an excellent indicator, a given girl being scored so many months before or after the menarche; the time of maximal velocity in height has also been most effectively used (Shuttleworth, 1937, 1938, 1939). Neither of these are available, however, except in retrospect; one cannot tell how much before the menarche a girl is until, obviously, she has reached it. In the circumstances considered in this paper two, or perhaps three, methods are available; these are the rating of secondary sex character development, the skeletal (wrist and hand) development, and, possibly, tooth eruption development.

Standards for secondary sex character (S.S.C.) development in the case of boys have been given in detail by Greulich and his associates (Greulich, Dorfman, Catchpole, Solomon and Culotta, 1942) Five stages are described, stage 1 being pre-pubertal, stage 2 beginning growth of testes, penis, pubic hair,

stage 3 a further development of testes, penis and pubic hair and often the beginning of facial hair, stage 4 further development again, with face hair definite and axillary hair beginning, and stage 5 near adult. These stages are, of course, far more fully described and illustrated by Greulich, so that a scaling on a rapid clinical examination should be perfectly feasible. For girls, similar scales for breasts and pubic hair separately have been illustrated by Reynolds and Wines (1948), and a rating combining the two characters would be simple to arrange. Since the breast and pubic hair begin developing about two years before the menarche on an average, S.S.C. ratings cover just the period when the adolescent spurt is maximal. (The menarche occurs shortly after the point of maximal velocity in stature.)

Several possible ways of incorporating these ratings into growth standards suggest themselves. First, simple standards for the time at which each stage occurs and the normal limits of this should be established; second, height and weight, and indeed all anthropometric standards during puberty, should be couched in terms of S.S.C. maturity group as well as, or instead of, chronological age; thirdly, regression standards using simply S.S.C. maturity ratings as one variable could be constructed; fourthly, a S.S.C. age could be developed in exactly the same way as skeletal age below.

Skeletal (Wrist-hand) Maturity. These standards go a little further. The maturation of the skeleton can be followed by x-rays and judged by whether such and such an epiphysis has appeared, whether another has closed, what shape a third has and so on. This skeletal maturation does not follow chronological age exactly, and especially at puberty the two part company. If the boy is an early maturer, his adolescent spurt in height and other anatomical and physiological measurements comes early, his secondary sex characters develop early and his bone appearances hasten to adulthood. Thus skeletal radiographs enable one to judge how far along in adolescence is a given child (and are quite closely related to S.S.C. groups in this), and they also, stretching back to birth, enable one to rate as mature beyond his years a child of any age whatsoever. The technique at present used is to take a radiograph of the left hand and wrist, a simple matter that can be very satisfactorily done with a small, portable dental machine. A set of standards is then consulted, the original one due to Todd (1937) having been recently superseded by a new edition from Greulich and Pyle (1950). Skeletal development has from the start been dealt with in the same way as mental age: a given boy's radiograph is matched to a particular standard and if that standard represents the development of the average boy of age $10\frac{1}{2}$, one lists the boy's skeletal age as $10\frac{1}{2}$ years. In practice the matching of films with standards demands a certain amount of skill and practice, and unfortunately wrist and hand changes seem to be minimal just at the beginning of puberty, thus tending to make the ratings least reliable and finely-spaced just when one wants the information most. The information one does get, however, is very valuable and this technique has deservedly gained a wide reputation for usefulness. Recently, a refinement of it, for use more in special than in general circumstances, perhaps, has been proposed by Pyle and her associates (Pyle, Mann, Dreizen, Kelly, Macy and Spies, 1948). In this, besides the whole appearance of wrist and hand being used to obtain the skeletal age, each individual bone or part in the radiographs is assigned a skeletal age and the range of the most advanced to the least advanced bone is given. This refinement is known, for historical reasons, as the red graph method. Malnutrition and certain other states are believed to increase the variability of maturation in the bones of hand and wrist besides retarding it generally.

The incorporation of skeletal maturity into general standards follows the same lines as that of S.S.C. maturity above (Bayley, 1943; Gray, 1948). It is not yet known to what extent the skeletal ages of American and British children are the same in terms of chronological age. Although the pattern of maturing is probably very similar in both countries, it may well be that the American children on whom the standards are founded are somewhat ahead of the average British child in maturity at any given age. If so, then while the average American child of chronological age $10\frac{1}{2}$ will have, being average, a skeletal age of $10\frac{1}{2}$ on the Greulich-Pyle standards, the British average child of $10\frac{1}{2}$ would have a skeletal age of somewhat less. No British standards are yet available.

Tooth Eruption Development. Tooth eruption development has not as yet been used as a measure of maturation, but there seems no good reason why it should not at least be tried; a measure of tooth age could readily be obtained, it would seem, from the figures in Palmer, Klein and Kramer's paper (1938) on the Hagerstown children or from Hellman's study (1943) in New York (see also Boas, 1933; Bengston, 1935; Doering and Allen, 1942; Meredith, 1946; Hurme, 1948). Tooth age would have its main application in the prepubertal years, and might be of particular interest as girls erupt their teeth somewhat earlier than boys, and this at a time when the sexes are otherwise little distinguished in development. Not much is known at

present about the relation of tooth eruption maturity to skeletal maturity.

Conclusion

It would be eminently satisfying if a survey of growth standards such as this started by propounding the statistical principles upon which such standards could be based, went on to list the inevitable results of their application with the appropriate data for use in each circumstance, and wound up with a few simple instructions in the use of a few master tests. But though satisfying, it would be at present wildly inappropriate. We lack as yet any comprehensive theory of the construction of normal standards involving numerous measurements all of which change as time passes, all of which are interrelated and most of which are not quite distributed in Gaussian form; some mathematical background exists (see for example, Box, 1950; Greenhouse and Mantel, 1950; Votaw, Kimball, and Rafferty, 1950; Wilks, 1941) but as yet it is a patchy one. We lack, for the most part, good series of standardizing data, at least for this country. And we are far from any simple and satisfactory general test of healthy growth in the child.

Summary

The current standards available for assessing whether or not a child is growing normally are presented and reviewed; the theoretical background and the limitations of each one are discussed.

The meaning of the assessment 'abnormal' is discussed, and the view presented that the assessor has in mind two populations, one healthy, the other unhealthy, probably overlapping; limits of normality are arbitrarily fixed for the purpose in hand, arranging inevitably to misclassify a certain proportion of normals as abnormal.

The relative merits of standards couched in percentile and in standard deviation terms are discussed.

The use of velocity or rate-of-growth standards as opposed to distance or size-at-age standards is advocated, and the use of standards for distance as though they were standards for velocity is deprecated.

No British velocity standards are available; the American ones are discussed.

The British and American distance standards available are reviewed and the opinion given that the currently best British height-weight standard data are those of Gore and Palmer for 0 to 5 years and Daley for 5 onwards, both being from London County Council children.

The use of height and weight only is deprecated and the optimal choice of a few measurements is discussed; the proper technique for taking heights and weights is given. No British standards exist for measurements other than height and weight; some of the relevant American data are reviewed.

The combination of two or more measurements into a standard is considered and its two possible regression forms, exemplified by weight-for-height-for-age and weight-for-height-irrespective-of-age, are presented. The use of each is discussed and the Wetzel grid and Tuxford's index shown to be special examples of such standards.

A suggested system of standards is presented tentatively for experimental trial; various measurements are considered in relation to age, and in relation to each other irrespective of age; both distance and velocity are tested for each measurement. The difficulty in interpreting multiple tests of this sort is stressed.

Standards for maturity, such as skeletal age by hand and wrist radiograph, secondary sex character, age and tooth development age are reviewed.

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A FAMILIAL CRISIS IN CONGENITAL ACHOLURIC JAUNDICE

BY

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A familial crisis in congenital acholuric jaundice involving several members of a family within a short space of time is an unusual occurrence. Nine further instances are reported by Barber (1934), Scott (1935), Murray-Lyon (1935), Dedichen (1937), Dameshek (1941), Lyngar (1942), Horne, Lederer, Kirkpatrick and Leys (1945), Owren (1948) and Marson, Meynell and Tarbush (1950). In the histories given below crises of varying severity are shown affecting five members of a family of seven. The family pedigree is illustrated in Fig. 1.

Case Reports

Case A. Beverley A, aged 4 years, was admitted to the Children's Hospital, Leicester Royal Infirmary, on September 27, 1950. The history showed that her illness began suddenly on September 21 when she vomited twice, became pale and listless, went off her food, became constipated, and complained of abdominal pain. On examination, besides the extreme pallor being noted, the child appeared listless and irritable. There was no jaundice. Her temperature was normal, pulse 100 and respirations 20. Small, shotty glands were palpable in the neck, axilla and groins, and the spleen was palpable two finger breadths below the costal margin; otherwise nothing abnormal was found.

On the day of admission a blood count showed Hb. 28% (4·5 g. %), red cells 1,800,000, colour index 0·78, white cells 18,500 (polymorphonuclears 90%, lymphocytes 8%, monocytes 2%). A blood film showed marked anisocytosis, spherocytosis and a large number of reticulocytes with occasional nucleated red blood cells.

Sternal puncture revealed a hyperplastic and normoblastic marrow.

Urine showed no haemoglobin, but *Bact. coli* was grown from a catheter specimen.

Her blood group was AII, Rh negative, and a transfusion of 170 ml. of packed cells was given at once in view of the severe anaemia. This raised the haemoglobin to 77% (12·32 g. %) and the red cells to 3,950,000. The urinary infection was treated with sulphamezathine and rapidly cleared.

When she had fully recovered from the crisis, on March 8, 1951, a blood count showed Hb. 67% (9·9 g.%), packed cell volume 29% (69% of normal), mean corpuscular diameter 6·4μ, mean corpuscular average thickness 3·1μ. A blood film showed marked spherocytosis. Total white cells, 10,800. A blood fragility test showed haemolysis beginning at 0·72% saline and complete at 0·32% saline (control beginning at 0·65% saline and complete at 0·36% saline). The serum bilirubin level was 1·4 mg. per 100 ml.

On examination at this time the child was well, she had a very slight icteric tinge to the sclera, and the spleen was palpable two to three finger breadths below the costal margin.

Case B. Anthony A, aged 3 years, was admitted to the Children's Hospital, Leicester Royal Infirmary, on October 5, 1950. The history revealed that eight days previously, that is eight days after the onset of illness in Case A, he had developed a cold and become listless. He had gone off his food and was thought to be fretting for his sister (Case A). The symptoms increased in severity and he became very pale, had no strength to play, complained of headaches and tiredness.

On examination the positive findings were: temperature 99·6° F., pulse 120, respiration 20, sclera slightly icteric and mucous membranes pale. There was generalized shotty enlargement of the lymph nodes. The spleen was palpable three finger breadths below the costal margin, and the liver one finger breadth.

The blood picture on October 6 showed Hb. 26% (4·16 g. %), red cells 1,750,000, colour index 0·74, white cells 11,000.

A blood film showed marked microcytosis and spherocytosis and small numbers of nucleated red blood cells. His blood group was AII Rh negative, and a transfusion of 200 ml. of packed cells was given. Afterwards the Hb. was 80% (11·9 g. %), red cells 4,180,000, colour index 0·97.

A full blood count was carried out on March 8, 1951, and found to be Hb. 59% (8·9 g. %), packed cell volume 27% (59% of normal), mean corpuscular volume 101 cμ, mean corpuscular diameter 6·5μ, mean corpuscular average thickness 2·9μ, white cells 3,900. Marked microcytosis and spherocytosis were seen in the blood film. The serum bilirubin level was 1 mg. per 100 ml. The urine showed no abnormality.

The blood fragility curve was typical of acholuric jaundice, haemolysis beginning at 0·88% saline and

complete at 0·28% saline (control 0·60% saline -0·32% saline).

On examination at this time the child's general condition was very good. The spleen was palpable two finger breadths below the costal margin.

As a result of a second case in the same family, the remainder of the family were sent for, and laboratory investigations gave the following results.

Family History

Case C. Martin A., aged 2 years, was not admitted to hospital, but about the time his sister and brother were admitted he was noticed to be pale and off colour. He was off his food and showed no interest in his toys. On examination he looked pale, but was well nourished. He seemed listless and tired. The only positive finding was that the tip of the spleen was palpable below the costal margin. A blood count on October 7 showed Hb. 40% (6·4 g. %), red cells 3,320,000, colour index 0·61, mean corpuscular diameter 6·43μ, white cells 6,600.

The blood fragility curve was typical of acholuric jaundice, haemolysis beginning at 0·88% saline and complete at 0·28% saline (control 0·60% saline -0·32% saline).

When he was seen on March 8, 1951, his general condition had much improved. He was lively and active and ate his meals well. On examination the mucous membranes were a very much better colour but the tip of the spleen was still palpable.

Case D. Mr. T. A. (father of Cases A, B, C and E) was a butcher. He gave a history of being subject to attacks of general malaise and had noticed that his eyes were frequently yellow-tinged. This had been recurring since he was a child, but the symptoms had never been severe enough to cause him to seek medical advice. At the time of the children's illness he noticed that the yellow tinge in his eyes had deepened. When seen on October 12, 1950, he was feeling quite well, but the sclera was markedly icteric. Apart from this nothing abnormal was found on examination, and the spleen was not palpable.

A blood count on October 7 showed Hb. 77% (12·32 g. %), red cells 4,450,000, colour index 0·88, packed cell volume 36%, mean corpuscular volume 81 cμ, mean corpuscular haemoglobin concentration 34%, mean corpuscular diameter 6·33μ, mean corpuscular average thickness 2·59μ.

The blood fragility curve showed haemolysis beginning at 0·84% saline and complete at 0·28% saline (control 0·60% saline -0·32% saline). The serum bilirubin level was 2·4 mg. per 100 ml.

Case E. Barry A., aged 7 years, was fit and well and did not complain of ill health during the time the other members of the family were ill. There was slight pallor of the mucous membranes, but no evidence of icterus and the spleen was not palpable.

A blood count on October 7, 1950, showed Hb. 62% (9·92 g. %), red cells 3,230,000, colour index 0·97, white cells 7,100. On March 8, 1951, Hb. 84% (12·4 g. %), packed cell volume 40% (95% of normal), mean corpuscular diameter 6·5μ, white cells 7,300. The blood film, however, showed no spherocytosis. The blood fragility curve showed haemolysis beginning at 0·88% saline and complete at 0·28% saline (control 0·64% saline -0.32% saline). The serum bilirubin level was less than 1 mg. per 100 ml. In view of the fact that no spherocytes were present in the blood film, the child must be considered a doubtful case of acholuric jaundice, but the family history, a slight degree of anaemia at the time when other members of the family suffered a crisis, small mean corpuscular diameter and slight increased fragility suggested that he might be a mild case.

As shown in Fig. 1 no evidence of acholuric jaundice was found in the other members of the family, and at the time of the familial crisis all were fit and well.

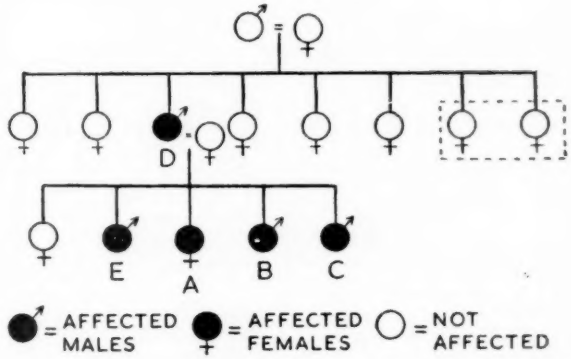

FIG. 1.—Pedigree of affected family. Siblings encircled in dotted lines had no symptoms. There are no records of them.

Discussion

Recently Marson *et al.* (1950) reviewed the literature and reported a family of seven in which four members underwent haemolytic crises within a short period. Two theories were put forward concerning the aetiology. The first was advocated by Owren (1948), who concluded that the crisis was due to a maturation arrest in the bone marrow causing aplasia, which, combined with the abnormal congenital condition of spherocytosis and thus a 14-day life span of the red cell (Dacie and Mollison 1943), caused the crisis. The second theory, that the crisis was due to the combination of a marked exaggeration of the usual haemolytic mechanism with arrested maturation of red cells in the bone marrow induced by a pathologically hyperactive spleen, was supported by Dameshek and Bloom (1948). Whichever aetiology is accepted some trigger mechanism is required to bring it into operation. In the case of familial crisis an infection would seem to be a possibility as it affects members living in close proximity and in the same environment. Dedichen (1937) has reported a series in

which a contagious respiratory infection was thought to be responsible. Horne *et al.* (1945) placed a ferret in the home in which a family crisis occurred and later the ferret died with symptoms of nasal catarrh and conjunctivitis. In the other cases reported infection was not a prominent feature, and emotion, as advocated by Piney (1931), appeared to have some association in three of the cases in Scott's (1935) series.

In this family no obvious infection was present. In Case A *Bact. coli* was present in the urine, but the child was afebrile and had no urinary symptoms. In Case B coryza was present at the onset, but the temperature was not raised above 99° F., and the degree of anaemia was thought sufficient to account for this. Indeed, in this case the mother felt the illness was due to the child fretting for his sister. The other members of the family had no obvious infection.

Recently Davidson, Duthie, Girdwood and Sinclair (1951) have shown that A.C.T.H. lowers the serum bilirubin level in congenital anaemia, and although clinical trials have not cured the condition, it is possible that the trigger mechanism may be associated with the reaction of the tissues to an antigen, and thus may be another disease associated in the stress syndrome.

Summary

A familial crisis affecting five members of a family with congenital acholuric jaundice is described. Consideration of this and other reported families does not support the view that infection is the trigger mechanism concerned.

I should like to thank Dr. W. Matheson for permission to publish these cases, and for his help in the preparation of this paper; also Dr. E. Milford Ward and the staff of the Pathological Department, Leicester Royal Infirmary, for the haematological investigations.

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FAMILIAL JAUNDICE OF THE NEWBORN ASSOCIATED WITH HEPATOSTEATOSIS

BY

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Jaundice in the neonatal period may be either present at birth or develop within the first few days of life. Since Levine and his colleagues demonstrated ten years ago the anti-Rh agglutinins in mothers of infants with icterus gravis, this form of jaundice, present at birth or developing within a few hours, has received a great deal of attention. Haemolytic disease of the newborn as a cause of icterus dominates diagnostic consideration, whereas congenital syphilis has lost in aetiological importance. Cirrhosis of the foetal liver has in rare cases been described as giving rise to jaundice at birth and leading to a fatal outcome within three to eight weeks. In addition, jaundice may be 'physiological' or due to septicaemia (Buhl's and Winckel's diseases), obliteration of the bile ducts or, more rarely, acholuric jaundice.

Two cases of congenital jaundice in siblings are here reported in which the pathogenesis differs from those already mentioned and which, to our knowledge, has not been previously recorded in the literature.

Case Reports

Case 1. M.K. was a full term male baby, born on May 12, 1947, after a forceps delivery. The forceps were applied because of delay in the second stage. The baby cried at birth and was noted to be jaundiced. The birth weight was 9½ lb. The mother was 23 years of age, para 2. Her diet had been adequate. Her health was good apart from some vomiting which persisted throughout the pregnancy. She had had infective hepatitis at the age of 20 but had completely recovered and there were no residual symptoms. Her Wassermann reaction was negative and she was Rh-positive. She had had a miscarriage at four months in April, 1946, the cause of which was unknown.

The baby was put to the breast six hours after birth and sucked satisfactorily and passed meconium normally. He continued to thrive until the fifth day when the mother noticed the jaundice to be much deeper. He then began to vomit his breast feeds and was lethargic. As a result of the continued vomiting and deepening jaundice, the mother sought medical advice and the baby was admitted to hospital on May 20, 1947, aged 8 days.

On clinical examination the baby was noted to be fairly well nourished and weighed 7 lb. 10 oz. having lost almost 2 lb. since birth. There was marked jaundice of the skin, conjunctivae and mucous membranes. The mouth was healthy, the abdomen was slightly distended, and there was a sero-sanguineous discharge from the umbilicus. The liver edge could be palpated in the right iliac fossa. The surface was hard, smooth and rather tender. The spleen was not palpable. There was a soft systolic murmur heard over the whole precordium. No abnormality was detected in any of the other systems.

A diagnosis of sepsis due to omphalitis was made and the infant was treated with penicillin, 12,500 units intramuscularly three-hourly, and sulphamezathine 0·5 g. four-hourly. A swab of the umbilical discharge grew coagulase positive *Staphylococcus aureus*. Vitamin K, 5 mg., was administered twice daily intramuscularly. The prothrombin level was 25%. Hb. was 134% (Haldane), i.e. 18·5 g. %; a red cell count gave 5·97 million/c.mm. The fragility test showed haemolysis beginning at 0·4% saline and complete at 0·25%. The baby was Rh-positive and the Coombs test was negative. The urine showed considerable quantities of bile and urobilin. The liver function tests gave the following results:

Thymol turbidity	1·5 units
Alkaline phosphatase ..	10·0 units
Serum bilirubin	7·8 mg. %
Cephalin-cholesterol flocculation	positive
Serum cholesterol	187 mg. %
Serum proteins	4·24 g. %
Albumin	3·09 g. %
Globulin	1·15 %
Albumin: globulin ratio ..	2·7

Attempts to perform the Wassermann test failed on two occasions owing to the fixation of complement in the absence of antigen.

During the next two days the jaundice gradually

became more intense, and the infant's skin assumed an olive green colour suggesting obstructive jaundice. However, the stools remained well coloured and contained bile and bile pigments. Vomiting persisted. By May 26 the baby had become very irritable, and by May 31 the general condition had markedly deteriorated and the liver was palpable well into the pelvis. At this time another mass became palpable in the left loin which was thought to be the left kidney. The vomiting ceased and the mother was again allowed to feed the baby, but by June 12 her milk was insufficient and the infant was changed over to a half-cream dried milk formula.

He fed less satisfactorily, the jaundice became very intense, he became stuporous and then comatose and finally died on June 14 at the age of 31 days.

POST-MORTEM REPORT. The body was that of a small, wasted child with a markedly jaundiced skin.

There was no congenital abnormality of the heart and blood vessels. The ductus and foramen ovale were closed.

There were a few small consolidated areas near the apex of the right upper lobe of the lung.

There was a slight excess of bile-stained fluid in the peritoneum. The stomach contained a fair amount of particles of altered blood; the contents of the large and small intestine were fluid. The duodenal contents were deeply bile-stained.

The liver (300 g.) was grossly enlarged. It was bright yellow and homogeneous throughout except in the right lobe where there was a circumscribed area approximately $1 \cdot 5 \times 1$ cm. which was of a lighter colour. The gall bladder was normal.

The spleen (18 g.) was slightly enlarged, dark and firm.

No abnormality was found in the adrenals, thyroid or thymus.

The kidneys (each 20 g.) were normal.

The surface of the brain was rather flattened and unusually pale. Beneath the dura over the right parietal region there was a small amount of clotted blood. The brain tissue on section was unusually pale, and the distinction between cortex and medulla poor. Pus was present in both mastoid cavities.

Microscopical examination of a right mastoid swab showed a few pus cells and Gram-positive cocci (some in short chains). On culture a heavy growth of haemolytic streptococci and *Staphylococcus aureus* (coagulase positive) was seen. A left mastoid swab also showed pus cells and streptococci, and on culture a heavy growth of haemolytic streptococci with a few coliform organisms.

In the liver microscopical appearances were those of practically complete fatty change so that no normal liver cells were present, a scaffold of liver tissue and portal areas only remaining. There was no round cell or polymorphonuclear infiltration. The liver cells were grossly vacuolated as by fat. There was much bile pigment, some in the liver cells and some forming small plugs in the bile canaliculi. In the portal tracts there was extensive proliferation of the bile ducts and many of these contained bile plugs. The periportal fibrous tissue was increased and extended outwards though not sufficiently to merit the term cirrhosis.

No significant abnormality was seen in the kidney.

The solid areas noted in the lung were pneumonic. In the alveoli the infiltrated cells consisted of polymorphs with a considerable proportion of large mononuclear cells. The condition was more extensive than naked eye examination had suggested.

Case 2. S.K. was a full term male infant, born on May 22, 1950, after a spontaneous delivery. Birth weight was 8 lb. He cried immediately and was noticed to be markedly jaundiced at birth. No other abnormality was detected on clinical examination except enlargement of the liver.

The mother's age was now 26. Her health during this pregnancy had been good. Delivery was uneventful and anaesthesia was not required.

The infant was lethargic from birth and refused to suck when put to the breast. He began to vomit bile-stained fluid. By the second day of life the liver was palpable three finger breadths below the right costal margin. The surface was smooth and regular and the edge was sharp. The spleen was not palpated. The depth of the jaundice increased. Vomiting continued and on the third day thrush appeared on the tongue and buccal mucosa. He lost weight rapidly. The Wassermann reaction and Coombs test were negative, and the blood, which was Rh-positive, gave Hb. 125% (Haldane), i.e. 17·2 g. %; white cells 9,400 per c.mm. (polymorphs 63%, lymphocytes 37%).

The infant continued to vomit throughout the fourth day and his lethargy was much more marked. During the succeeding three days there was no improvement, the jaundice deepening further. He was increasingly sleepy but the liver remained the same size and consistency and the spleen was not palpable. By the eighth day his condition had further deteriorated. He had become comatose, the skin and mucous membranes were a deep yellow, the head was retracted, fists were clenched, and though the fontanelle tension was normal, a diagnosis of cerebral birth trauma was entertained. Lumbar puncture was performed and examination of the fluid, which was barely opalescent, gave red blood cells 40 per c.mm., polymorphs 1 per c.mm., protein 80 mg. %, chlorides 770 mg. % and sugar 80 mg. %.

The coma persisted and he died on June 3, 1950, aged 8 days.

POST-MORTEM REPORT. The body, that of a male child, was cyanosed and jaundiced. There were no other external abnormal findings.

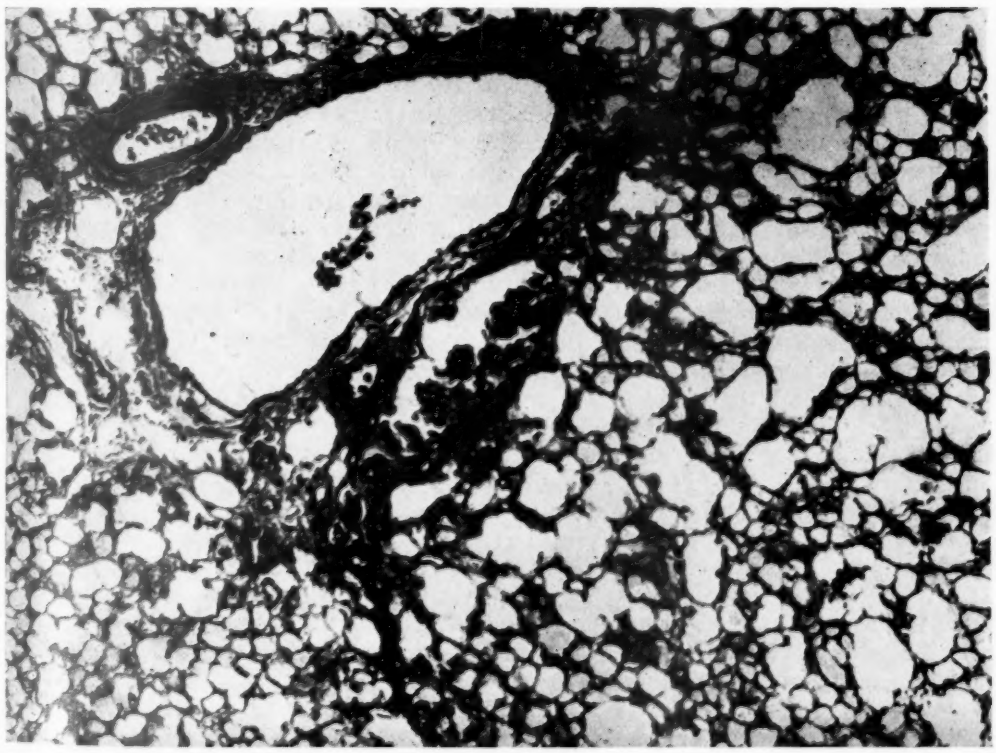
The heart (40 g.) was of foetal shape, and the ductus arteriosus was widely patent. The orifices and valves were normal. The myocardium was pale but firm.

The left lung (40 g.) was completely atelectatic, and in the right lung (60 g.) there was considerable patchy collapse. Both pleural cavities contained blood-stained fluid, and the trachea and right bronchus were full of thick mucus.

The oesophagus, stomach and gut were normal. The liver (200 g.) was enlarged and a deep golden colour. The consistency was that of putty. The pattern was lost, and the bile ducts were patent. The pancreas and spleen were normal.

FIG. 1.—Section of liver of M.K. showing complete fatty change.

FIG. 2.—Section of liver of S.K. showing destruction of normal liver tissue by deposits of fat.



The kidneys (40 g. together) showed a swollen and yellowy cortex, of which the pattern was indistinct. The genital ducts, bladder and urethra were normal.

The brain, which was diffluent, was apparently normal.

Microscopically the liver showed extensive vacuolation of the cells, as by fat. Some pigmentation was present; near the portal tract it was probably formalin pigment. There was no increase in fibrous tissue or bile duct proliferation. Osmic acid and Sudan III staining of liver sections showed that the cells contained fat.

On special staining sections of the spleen and kidney showed no amyloid. Chemical analysis of the liver fat gave the following results:

Total fat	17% (as total fatty acids)
Neutral fat	76% of total fat
Cholesterol	0·88%
Total phospholipids ..	4·2%

Discussion

Fatty liver in the newborn has been encountered in Buhl's disease as part of the widespread fatty degeneration of parenchymatous organs in this condition, which is now commonly regarded as a form of neonatal septicaemia.

Haemorrhagic manifestations and severe asphyxia, leading to marked cyanosis and jaundice, are the outstanding manifestations of the clinical picture of Buhl's disease. With improved hygiene and care in maternity units and obstetric wards of hospitals it has become a rarity. The absence of asphyxia, cyanosis and haemorrhages differentiate it from the cases reported here. Jaundice may appear early in this condition but is not present at birth. Though Buhl's disease occurs sometimes in small epidemics it has not been reported in siblings.

Infection was present in the older of the siblings, but it appeared only after five days in the course of the primary illness and it is a fair assumption that this was superimposed, since delivery took place in the patient's home where hygiene may not have been adequate. The younger of the siblings, born in a modern maternity unit, did not show any signs of septicaemia or gross localized infection. Listlessness, failure to suck, inability to cry, jaundice and liver enlargement were evident from birth and have to be attributed to the single outstanding pathological finding, almost identical in both cases, hepatosteatosis.

The earliest report on the familial form of fatty liver as a cause of death in infancy was by Björum (1926) who described four cases in a family of 11 children. However, his cases differ in certain important aspects from those recorded here, in that jaundice was absent and none of his cases occurred in the neonatal period. The youngest was an infant who died at the age of 5 months and the oldest was 2 years. The liver was examined microscopically in the case of the 5-month-old infant and the cytoplasm of the liver cells was completely filled with fat. There were no changes in the nuclei but perhaps a slight increase in the interstitial tissue round the lobules.

In Britain Smith and O'Flynn (1933) presented two cases of familial hepatomegaly in a 6-year-old child and a 20-months-old infant. The six-year-old child had first come under observation at the age of 15 months. He was undersized, fat and flabby. The abdomen was enormously distended by the very large liver. He died suddenly after a bout of coughing. Jaundice was absent throughout his illness. At necropsy the liver was grossly enlarged, smooth, firm and pale buff. On sectioning, the cut surface appeared smooth and homogeneous with the exception of several minute yellow areas. On Scharlach-red staining the section showed large empty cells with preservation of the nucleus. No fat, lipoid or double refractive material was detected in the cells. Clearly this was not a case of fatty liver and the biochemical analysis of the liver (dried matter, 1·202%, cholesterol 0·728%, cholesterol esters 0·060%, fat and fatty acids 0·414%) supports this opinion.

An interesting instance of hepatic steatosis was recorded by Debré and Semelaigne (1930) in an infant 9 months old who developed severe anorexia at the weaning period and in consequence suffered extreme loss of weight. The liver was grossly enlarged, and a small portion was removed for biopsy at laparotomy. On section most of the liver cells were seen to be invaded by large droplets of fat, the nuclei being compressed to one side. The portal spaces were the site of lymphoid infiltration. Signs of hepatic failure appeared at one stage, with the development of jaundice, purpura and urobilinuria, but finally the infant made a complete recovery.

Jaundice in the neonatal period, associated with hepatomegaly but not present at birth, has been reported in cases of galactosaemia by Bruck and Rapoport (1945), Göppert (1917), Goldbloom and Brickman (1946), Goldstein and Ennis (1948) and by Donnell and Lann (1951). But melituria, cataract, albuminuria and inanition help to mark it as a definite clinical entity. Hepatomegaly with marked steatosis occurs in von Gierke's disease but is not associated with severe congenital icterus, though a slight transitory jaundice may occur during the first month of life (Thannhauser, 1950).

Fatty liver in infancy is not an infrequent post-mortem finding in children dying of toxic or infective conditions and chronic wasting diseases such as tuberculosis and diabetes. Massive steatosis in gastro-enteritis had been described by, among others, Marfan (1923), Marie, Seringe, Schweisguth

and Hébert (1947) and Lévesque, Lafourcade and Demassieux (1947).

Fatty liver as a result or complication of severe forms of malnutrition has also been found in the infants and children of various tropical and subtropical countries. It is one of the outstanding pathological findings in kwashiorkor as encountered in West Africa, in the infantile pellagra as described in South Africa and studied by Gillman and Gillman (1945 a and b). Waterlow (1948) investigated forms of malnutrition in the West Indies and refers to the condition as 'fatty liver disease', since fatty liver was regarded as the most important and dominating morbid anatomical observation. Similarly liver steatosis in undernourished children was reported from Chile by Meneghello, Niemeyer and Espinosa (1950). The large majority of the cases reported occurred after the first six months of life and usually in the second and third year. Jaundice is not a feature of the condition, which varies somewhat in its symptomatology according to its regional distribution, though marasmus, nutritional oedema and fatty liver seem manifestations common to all of them. However, none of the conditions described above appear to bear any relationship to the familial form of fatty liver in the neonatal period.

Waterlow (1948) found in chemical estimations of the fat content up to 50% of the fresh weight of the livers examined. A striking finding was the great increase in neutral fat. In Chile, Niemeyer and Iturra (1947) demonstrated an increase of total lipids to 20% of the net weight of the liver, most of the fat accumulated being formed by triglycerides. Phospholipids increased also but became stabilized at 4% and cholesterol at 1%. Phospholipid values in Waterlow's cases ranged between 0·4 g. and 2·2 g. per 100 g. fat-free, dry weight.

Comparative data on the fat content of livers in normal and diseased children in Europe are scanty. The liver of an infant aged 5 days who died of cerebral haemorrhage was therefore also examined biochemically and the following figures were obtained:

Total fat	14% (as total fatty acids)
Neutral fat	4·5%
Cholesterol	2·1%
Total phospholipids ..	11·3%

Thannhauser (1950) gives the following results for the fat analysis of the normal liver of an 8-months-old infant:

Neutral fat	3·4–3·9%
Total cholesterol	0·4–0·6%
Cholesterol esters	0·1–0·2%
Free cholesterol	1·19%
Total phospholipids	5·4–6·3%
Fatty acids	7·2–8·5%

This was compared with the fat analysis of liver in Case 2. The chief features are the increase in total fat, the high percentage of neutral fat and the low percentage of cholesterol and phospholipids.

Histologically there was a remarkable similarity in the appearance of the liver in both cases except that in Case 1 the process seemed to have progressed further. There was a complete disorganization of the liver structure, and indeed it was difficult to recognize the section as such. Only small areas of liver tissue were preserved and the function of the organ must have been severely impaired.

The maternal history did not reveal any dietary deficiency during pregnancy which might have suggested inadequate intake of the lipotropic factors. No drugs were administered or taken without advice, nor was there any evidence that the mother had suffered from poisoning with any of the substances that may induce fatty liver. Though she had chloroform anaesthesia for a short time during the birth of the first child, no use was made of an anaesthetic during delivery of the second. The possibility of a fat storage disease similar to glycogen disease has therefore to be considered, be it due to absence of lipotropic factors or inhibition of certain enzyme systems. Whatever the pathogenesis, it must have affected the liver and its fat metabolism specifically, since both children developed in other respects normally *in utero* and had relatively high birth weights.

Summary

Two cases of jaundice present at birth occurring in the same family were reported.

Jaundice was associated and assumed to be due to marked hepatosteatosis which developed *in utero*.

Clinically the picture was that of jaundice at birth with gross liver enlargement, apathy, listlessness and anorexia leading to coma and death.

The chemical analysis of liver tissue showed an increase in the total fat, particularly of the neutral fat fractions (76%) with reduction in the phospholipids and cholesterol.

The relative literature is discussed and no previous reports of jaundice at birth due to fatty liver are traced.

Our thanks are due to Professor Wilfrid Gaisford for his interest and valuable criticism, to Dr. F. A. Langley and Dr. S. H. Jackson for the post-mortem and histological reports, to Dr. W. H. Patterson and Dr. M. L. Thomson for the loan of the notes of Case 1, and to Mr. H. Varley for the biochemical investigations.

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THE RELATION OF BLOOD PRESSURE TO WEIGHT, HEIGHT AND BODY SURFACE AREA IN SCHOOLBOYS AGED 11 TO 15 YEARS

BY

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In striking contrast to the abundant information we possess about the 'normal' blood pressure (B.P.) in adults our knowledge of what might be considered as the normal range of B.P. in school children is limited, and owing to the various methods used, of little avail for comparison. Blood pressure reading is not part of routine medical inspection, although it has been known for a long time that a normal person reaches his mature B.P. at about adolescence (Robinson and Brucer, 1939) and that the incidence of hypertension is as high at the age of 15 as it is at the age of 40 (Alvarez and Stanley, 1930). Hines (1937), using the 'cold-test', found 18% hypertension among schoolboys. The question of an early onset of essential hypertension is, therefore, a problem of preventive medicine. Yet, what is to be considered as the upper normal limit for the various years of age in this group? This problem is quite apart from the more important question of what is normal for the individual, which seems to receive confusingly discrepant answers. Robinson and Brucer (1939), in an investigation of 11,383 persons, described as the normal range for men and women of any age 90-120 mm. systolic and 60-80 mm. diastolic. Alvarez (1920) found an average of 126 mm. in 16-year-old boys, and in 15,000 students 45% with a systolic pressure over 130 mm. and 22% over 140 mm. Kylin (1937), in persons under 40 years, found a normal range of 90-130-140, and Hahn (1924) for the age group 10-40 years a mean of 119·2 and a standard deviation of 15·9 mm. Paterson and Moncrieff (1949) stated as the upper limit a systolic B.P. of 110 mm. for 10-year-old and 120 mm. for 14-year-old boys, regarding a B.P. as abnormal which is persistently 20 mm. higher than the upper limit of the norm for the age. Taussig and Hecht (1938) reported as normal ranges for 10-year-old children 95-110 systolic, 60-70 diastolic; for 12-year-old children 102-115 systolic, 62-72 diastolic, and in 14-year-old children 104-124 systolic, 65-78 diastolic. Müller (1921), describing basal B.P. values for 11-14-year-old children, gave 80 mm. systolic as night, and 100 mm. as day, values for the systolic B.P.

In a preliminary report (Hahn, 1951) on the B.P. readings in 770 boys aged 11 to 15 years I was able to demonstrate that if we regard 90-130 mm. Hg as the normal range of systolic B.P. the percentage of hypertension is as high as 16·2 in the 14-year-old and 26·6 in the 15-year-old boys. I was then faced with the problem whether, in view of the clinical and somatotypical aspect of the hypertensive group, the term 'hypertension' was really justified, or if in fact our notion about the normal range of B.P. in this age group should be revised. It soon became apparent that the boys with the best physique, mainly belonging to Kretschmer's athletic or pyknic type (as far as the latter type is recognizable at this age), fell into the 'hypertensive' group, and, notwithstanding the similarity of their somatotype to the physique usually present in the hypertensive adult, their B.P. appeared to be rather a functional correlative to the supernormal deviation of growth in general. The problem of normal and abnormal B.P. thus became a question of individual normality or abnormality and led to a statistical study of the relation between B.P. and anthropometric measurements in the age group under consideration.

In eight senior schools in the City of Leicester 1,417 boys were examined. All the measurements were carried out by one observer, myself. It is the purpose of this paper to establish standard figures based on the correlation of blood pressure, weight,

height and body-surface area to determine whether in a given individual of this age group the B.P. is within normal limits.

Material and Method

Blood pressure readings were taken in the course of routine medical inspections, and all boys falling into the age group 11-15 years were examined. As the eight schools are scattered over the city, the sample includes boys coming from families of all social classes and can be considered a fair cross-section of an urban population. Excluded from the survey were cases with a history of renal disease, congenital and rheumatic heart disease, and hyperthyroidism. It is obvious that it was impossible to avoid the inclusion of pathological hypertensive cases due to such rarer causes as, for example, unilateral renal hypoplasia. Although basal B.P. measurements could not be achieved, care was taken that standard conditions were maintained. The reading was performed in the morning, always at the end of the routine examination, never after exercise, and in the sitting position. The sphygmomanometer used was Recklinghausen's tonometer gauged by a mercurial manometer. It must be stressed that, in contrast to similar investigations in adults, little apprehension was noted in the boys to whom the procedure was explained before the reading. The recommendations given in the report of the Joint Committee of the Cardiac Societies of Great Britain and America (1939) were followed. Three successive readings were taken, and the lowest value of systolic and diastolic pressure used for statistical evaluation. Whenever the B.P. appeared to be high, the reading was repeated the next morning, in some cases a third time two days later.

Results

The age distribution of the 1,417 boys is set out in Table 1.

The distribution is uneven as mostly 'leavers' and new entrants were examined, and thus, if a greater sample of 12-, 13- and 15-year-olds was reviewed, slight correction of the data for these three ages might be expected.

Table 2 records the mean ± standard error (S.E.), the standard deviation (σ), the difference of the means, the coefficient of variation (C.V.) and the absolute range of systolic and diastolic B.P.

It can be seen from this table that, while in the 12-year-old boys the systolic mean is almost the same as in the 11-year-old boy, there is a rise in the mean systolic pressure from 13·5 years onwards, the age when puberty starts. The increase between 12·5 and 13·5 and between 13·5 and 14·5 exceeds by four times the standard error of the difference of the means.

TABLE 1

AGE DISTRIBUTION OF SAMPLE

Central age in years	11·5	12·5	13·5	14·5	15·5	Total
Number of Boys	211	126	118	880	82	1,417

TABLE 2

SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN 11 TO 15-YEAR-OLD BOYS

Central Age	No.	M.±S.E.	σ	Difference of Means	C.V.	Range
		A. Systolic				
11·5	211	108·5±0·76	11·1		10·2	75–140
12·5	126	109·3±1·11	12·5	+0·8	11·4	80–145
13·5	118	113·5±1·31	14·2	+4·2	12·5	83–155
14·5	880	118·4±0·47	13·9	+4·9	11·7	80–175
15·5	82	119·1±1·74	15·8	+0·7	13·3	85–170
		B. Diastolic				
11·5	211	62·6±0·53	7·7		12·3	40–75
12·5	126	62·0±0·71	8·0	−0·6	12·9	40–85
13·5	118	62·9±0·8	8·7	+0·9	13·8	40–80
14·5	880	67·0±0·31	9·1	+4·1	13·6	35–100
15·5	82	69·2±0·89	8·1	+2·2	11·7	50–90

C. Pulse Pressure (average)					
Central age	11·5	12·5	13·5	14·5	15·5
Pulse pressure (mm. Hg)	47·2	45·8	50·7	51·3	51·7

The changes of the diastolic blood pressure are much less conspicuous, showing a significant rise in the 14- and 15-year-old boys.

The pulse pressure is slightly higher in the 13 to 15-year-old boys, and the difference between this group and the prepubertal group is statistically significant.

Table 3 gives the percentage distribution of systolic and diastolic blood pressures for each year.

Fig. 1 illustrates that the peak of the frequency of the systolic blood pressure is shifted to the right in the 14- and 15-year-old boys and that the distribution curve becomes flatter in the 15-year-old boys.

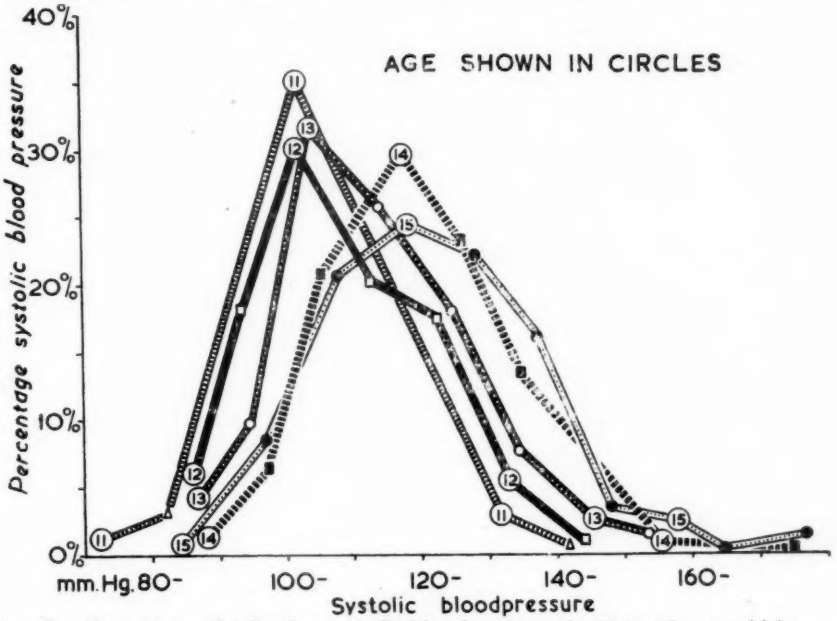

FIG. 1.—Percentage distribution systolic blood pressure in 11 to 15-year-old boys.

TABLE 3
PERCENTAGE DISTRIBUTION OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN 11 TO 15-YEAR-OLD BOYS

Central Age	11·5		12·5		13·5		14·5		15·5	
(mm. Hg)	No.	%	No.	%	No.	%	No.	%	No.	%
				Systolic						
70–79 ..	2	1·0	0	0·0	0	0·0	0	0·0	0	0·0
80–89 ..	6	2·9	7	5·6	5	4·3	10	1·1	1	1·2
90–99 ..	40	19·0	23	18·2	11	9·3	54	6·1	7	8·5
100–109 ..	75	35·4	38	30·1	37	31·3	182	20·7	17	20·7
110–119 ..	50	23·7	28	22·2	30	25·4	261	29·7	20	24·4
120–129 ..	31	14·6	22	17·5	21	17·9	202	23·0	18	22·0
130–139 ..	6	2·9	7	5·6	9	7·6	120	13·6	13	15·9
140–149 ..	1	0·5	1	0·8	3	2·5	37	4·2	3	3·7
150–159 ..	0	0·0	0	0·0	2	1·7	8	0·9	2	2·4
160–169 ..	0	0·0	0	0·0	0	0·0	5	0·6	0	0·0
170–179 ..	0	0·0	0	0·0	0	0·0	1	0·1	1	1·2
Total ..	211	100·0	126	100·0	118	100·0	880	100·0	82	100·0
90–129 mm.		92·7%		88%		83·9%		79·5%		75·5%
130 and above		3·4%		6·4%		11·8%		19·4%		23·3%
140 and above		0·5%		0·8%		4·2%		5·8%		7·4%
				Diastolic						
30–39 ..	0	0·0	0	0·0	0	0·0	1	0·1	0	0·0
40–49 ..	13	6·2	5	4·0	6	5·1	14	1·5	0	0·0
50–59 ..	56	26·5	42	33·3	38	32·2	169	19·2	10	12·2
60–69 ..	109	51·7	57	45·2	53	44·9	387	44·1	34	41·5
70–79 ..	33	15·6	19	15·1	17	14·4	249	28·4	33	40·3
80–89 ..	0	0·0	3	2·4	4	3·4	54	6·1	4	4·8
90–99 ..	0	0·0	0	0·0	0	0·0	5	0·5	1	1·2
100–109 ..	0	0·0	0	0·0	0	0·0	1	0·1	0	0·0
Total ..	211	100·0	126	100·0	118	100·0	880	100·0	82	100·0
40–79 ..		100·0%		97·6%		96·6%		93·1%		94·0%
80 and above		0·0%		2·4%		3·4%		6·8%		6·0%

From Table 3 it can be seen that whereas the percentage of systolic blood pressure for the range 90-129 is over 90% in the 11-year-old boys, this percentage decreases steadily to 88, 83·9, 79·5 and 75·5 in the following years of age. If values over 130 mm. were to be considered as hypertensive, the respective figures for the 13-, 14- and 15-year-old boys are climbing from 11·8 to 19·4 and 23·5%; 78·1% of the 11·5 and 70·5% of the 12·5-year-old boys have a systolic blood pressure between 90 and 119 mm., while three-quarters of the 13·5- and 14·5-year-old-boys show a systolic blood pressure between 100 and 129 mm. Of the 15·5-year-old boys, 62·3% have a systolic blood pressure between 110 and 139 mm.

For the diastolic blood pressure the range of highest frequency is much more limited. For all the ages concerned, the percentage covering the range 40-79 is over 90% and values above 80 mm., which could be considered as diastolic hypertension, reach 6·8 and 6·0% in the 14·5- and 15·5-year-old boys only.

Of the 11·5-, 12·5- and 13·5-year-old boys 78·2, 78·5 and 77·1% have a diastolic blood pressure between 50 and 69 mm., while 72·5 and 81·8% of the 14·5- and 15·5-year-old boys fall within the range of 60 to 79 mm. diastolic blood pressure.

Correlation between Systolic and Diastolic Blood Pressure

The diastolic blood pressure, as can be observed from the values of the pulse pressure given in Table 2, follows the pattern of the systolic blood pressure, i.e. rises with it. The correlation coefficient and the regression equation was determined for each age group and the results are given in Table 4.

in one characteristic for a unit change in the other. Thus, the diastolic blood pressure rises if the systolic pressure increases by 10 mm. Hg for the following ages :—

11-year-old by 3·3 mm. Hg
12-year-old by 4·1 mm. Hg
13-year-old by 4·0 mm. Hg
14-year-old by 2·9 mm. Hg
15-year-old by 2·1 mm. Hg

From the equation given in the last column of Table 4 the diastolic blood pressure corresponding to a given systolic value can easily be predicted.

Blood Pressure and Growth

The survey so far has shown that in the average boy B.P. ' spurts ' at about 13·5 years of age, that is when puberty has set in, with its dramatic bodily changes characterizing the third period of acceleration of growth. But variation is more than ever at work and no rigid pattern can be observed. Genetically determined it is the constellation of the whole ensemble of the ductless glands which, under the direction of the anterior lobe of the pituitary, will decide for the individual boy not only the onset but also the extent of the phenomena that are produced by the impact of the hormones released by the pituitary gland. Environmental influences, too, will interfere in a positive or negative direction and thus height and weight as well as functional features vary from boy to boy during this revolutionary period of life. The blood pressure follows the pattern of growth and its rate of increase is governed by the laws of the boys' constitution. The physiological, not the chronological, age is decisive for the place he is to achieve with regard to his physique and his blood pressure.

Blood Pressure and General Condition. It has been mentioned before that if in a rough and ready

TABLE 4

CORRELATION BETWEEN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN 11 TO 15-YEAR-OLD BOYS

Central Age	No.	Corr. Coeff.	S.E.	Regression Coeff.	Diastolic B.P.*
11·5	211	+0·499	±0·068	0·332	=0·33 × syst. + 25·7
12·5	126	+0·658	±0·083	0·405	=0·41 × syst. + 17·2
13·5	118	+0·646	±0·092	0·396	=0·40 × syst. + 17·5
14·5	880	+0·44	±0·033	0·288	=0·29 × syst. + 32·8
15·5	82	+0·412	±0·11	0·211	=0·21 × syst. + 44·2

* Calculated from regression equation.

As can be seen from Table 4 the correlation between systolic and diastolic blood pressure is positive for all ages and significant as shown by the standard error. The regression coefficient demonstrates the change which, according to the line representing the regression equation, takes place

way a B.P. of 129/79 is regarded as the upper limit of normal for the age-group under consideration, the boys belonging to the ' hypertensive ' group were in the majority conspicuous for their good, very often excellent physique. Furthermore, and here nutrition may be the decisive factor, it could be

noticed that the average systolic B.P. of boys in schools serving districts of lower income groups was distinctly lower than the respective values for boys coming from higher income groups.

As a practical preliminary step it seemed profitable to assess the relation of B.P. to physique by comparing the general condition in hypertensive and non-hypertensive boys using the customary grading in the medical inspection schedules. 'A', 'B' and 'C' thereby denote 'good', 'fair' and 'poor' according to the impression the observer obtains from nutrition, muscle tone, turgor and vascularization of the skin, posture, facial expression and mental alertness of the examinee. This evaluation, though necessarily subjective in its nature, should be admissible if employed by one observer only, as was the case in the sample under consideration.

In Table 5, 880 boys, of 14 years of age, hypertensive and non-hypertensive, are tabulated according to their systolic B.P. and general condition.

The difference between the proportions of A in hypertensives and non-hypertensives is 19·1%; as the standard error of the difference between these two proportions is 3·6%, the difference can be considered as highly significant. The mean of the systolic blood pressure is significantly higher in the A group than in the B group, whilst the diastolic B.P., being 72, 72 and 71 mm. respectively, is practically the same in all groups.

Blood Pressure, Weight and Height in 11 to 15-Year-old Boys

The features of growth before and in puberty are well known and it is not proposed to discuss them here in detail. Table 6, which gives the statistical data, demonstrates the spurt in weight and height starting at about 13·5 years of age. Considering the relatively small volume of the sample, the values obtained are well in conformity with the standard

TABLE 5
GENERAL CONDITION IN 880 BOYS

		A (Good)	B (Fair)	C (Poor)
Total	880	11·9%	67·1%	21·0%
Hypertensives	172	27·3%±3·39%	64·5%	8·2%
Non-hypertensive	708	8·2%±1·03%	67·8%	24·0%
Mean systolic B.P. in		127·5 ±1·15	119·0 ±0·52	110·8 ±0·95

TABLE 6
WEIGHT AND HEIGHT IN 11 TO 15-YEAR-OLD BOYS

Central Age	No.	M.	S.E.	σ	C.V.	Range
			Weight			
11·5	211	35·03 77·1 lb.	±0·35 kg.	5·12 kg. 11·3 lb.	14·6	25·5–53·6 kg. 56–118 lb.
12·5	126	36·4 80 lb.	±0·62 kg.	6·9 kg. 15·2 lb.	18·9	22·3–72·2 kg. 47–158 lb.
13·5	118	41·5 91·3 lb.	±0·76 kg.	8·2 kg. 18·04 lb.	19·7	27·7–63·6 kg. 61–140 lb.
14·5	880	46·65 102·5 lb.	±0·30 kg.	8·96 kg. 19·7 lb.	19·2	29·5–81·8 kg. 64·9–178 lb.
15·5	82	52·8 116·2 lb.	±1·06 kg.	9·6 kg. 21·1 lb.	18·1	31·8–75·9 kg. 70–177 lb.
			Height			
11·5	211	140·2 56·1 in.	±0·44 cm.	6·35 cm. 2·5 in.	4·4	127–156 cm. 50·8–62·4 in.
12·5	126	143·8 57·6 in.	±0·71 cm.	7·95 cm. 3·2 in.	5·5	125–175 cm. 50–70 in.
13·5	118	150·5 60·2 in.	±0·75 cm.	8·1 cm. 3·24 in.	5·4	127–170 cm. 50·8–68 in.
14·5	880	156·5 62·6 in.	±0·30 cm.	9·0 cm. 3·6 in.	5·7	122·5–182·5 cm. 49–73 in.
15·5	82	162·8 65·1 in.	±1·09 cm.	9·8 cm. 3·9 in.	6·0	137·5–185 cm. 55–74 in.

figures presented in larger statistics, as for instance in the recently published work of Sutcliffe and Canham (1950).

As shown in Table 6 the average increase in weight is 1·4 kg. and in height 3·6 cm. between 11·5 and 12·5 years and rises to 5·1, 5·2 and 6·1 kg; 6·7, 6·0 and 6·3 cm. for the ages 12·5-13·5, 13·5-14·5 and 14·5-15·5. Yet the steady rise of the standard deviation after the beginning of puberty illustrates the well established fact that, during this critical period, boys of the same age differ considerably in their growth; some reach puberty before 13·5 years and many lag behind and have not attained puberty at the age of 15 years, which, for British boys is the median age at which adolescence is attained (Ellis, 1950). In weight and height these latter boys often represent the average values of a 12- or 13-year-old boy; in other words, their physiological age or their weight- or height-age is that of a boy of 12 or 13 years.

Blood pressure in this age group follows the same pattern as can be seen in Fig. 2 giving the average values of weight, height and B.P. for the years 11·5 to 15·5.

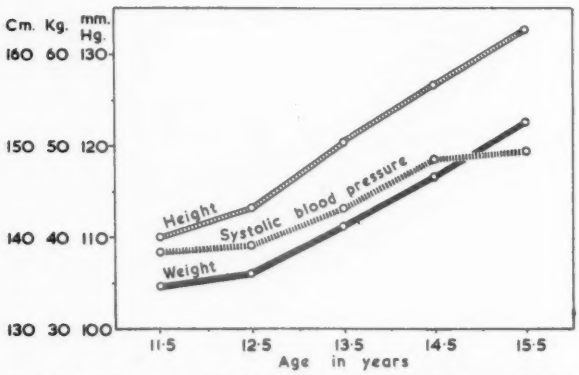

FIG. 2.—Mean systolic blood pressure, weight and height in 11 to 15-year-old boys.

In adults there is a correlation between hypertension and overweight (Koller, 1936). Robinson and Brucer (1940), in a study of B.P. and body build based on the findings in 3,658 persons, found a positive correlation between body build and B.P., men and women of 'lateral or broad build' sthenic type representing systolic hypertension four times as frequently as the asthenic, linear type, and diastolic hypertension seven times more frequently.

In order to ascertain whether there is any correlation between weight, height and B.P. within their respective natural variations, the correlation coefficients (r) were calculated. The results for each age group are given in Table 7.

In all five ages the correlation coefficient is positive both for B.P. and weight and B.P. and height and exceeds twice the standard error of the correlation coefficient. The association is closest for B.P. and weight and B.P. and height in the 13·5-year-old boys. From the regression equation as given in Table 7 it is possible to predict the systolic blood pressure which to a certain degree appears to be normal for a given weight or height. As an example values for the systolic blood pressure for each year of age obtained in such a way are computed in Table 8.

It can be observed that in the central part of Table 8, within an area covering roughly the range between M−1S.D. and M+1S.D. of the weight representing the respective year, the expected values of systolic blood pressure differ only slightly for the same weights irrespective of age. Thus a boy appears to have the blood pressure of his physiological age as it is manifested in his weight. Take, for example, a boy whose age is 14·5 and whose weight is 35 kg. (5 st. 7 lb.), his physiological age is then (Table 6), according to his weight, about that of the average 11·5-year-old boy and his systolic B.P. that of the average 11·5-year-old, i.e. 108·5 mm. As his weight deviates from the mean of his age by −11·6 kg., his blood pressure should deviate from the mean of his age (Table 2) by $-11\cdot6\times0\cdot6$, i.e. −7 mm., which means 111·4 mm. expected B.P. (Table 8 gives the value 111·4 mm. Hg). Suppose that the weight of a 14·5-year-old boy is 53 kg., i.e. the mean weight of 15·5-year-old boys whose mean systolic B.P. is 119·1, his expected B.P. therefore, according to the regression equation for his age, is 122·2, and according to the equation for the 15·5-year-old boys, 119·2 mm. Hg, which shows that the formula corresponding to his weight-age should be applied.

Comparison of the expected systolic B.P. ±5 mm. Hg with the actual systolic B.P. readings suggests that the normal B.P. for boys with proportionate weight and height measurements can be predicted by using the regression equations. In boys, however, with either excessive weight, as in cases of pituitary obesity, or excessive height, as in hypogonadism, the formulae are not always applicable as in both conditions there is a tendency to arterial hypotension. The fact that boys belonging to those groups are included in the statistical evaluation of this survey makes it probable that by using a much greater volume as basis for the calculations corrections will occur.

Blood Pressure and Body Surface Area

Considering the association which exists between systolic B.P. and weight and height, the use of one

TABLE 7

DATA RELATING BLOOD PRESSURE, WEIGHT AND HEIGHT

Central Age	No.	Corr. Coeff. ± S.E.	Regr. Coeff.	Regression Equation
		Weight		
11·5	211	+0·242±0·068	0·56	syst.−108·5=0·56 (wt.−35·0)
12·5	126	+0·411±0·083	0·78	syst.−109·3=0·78 (wt.−36·4)
13·5	118	+0·511±0·092	0·89	syst.−113·5=0·89 (wt.−41·5)
14·5	880	+0·400±0·033	0·61	syst.−118·4=0·6 (wt.−46·7)
15·5	82	+0·322±0·11	0·512	syst.−119·1=0·5 (wt.−52·8)

Systolic blood pressure as calculated from the regression equation

Central age	**11·5**	**12·5**	**13·5**	**14·5**	**15·5**
Systolic B.P. :	=0·56×wt.+88·9 ;	0·78×wt.+80·9 ;	0·89×wt.+76·3 ;	0·6×wt.+90·4 ;	0·5×wt.+92·7
With each kg. rise in weight B.P. rises by ..	0·56 mm.	0·78 mm.	0·89 mm.	0·6 mm.	0·5 mm.

		Height		
11·5	211	+0·229±0·068	0·429	syst.−108·5=0·43 (ht.−140·2)
12·5	126	+0·299±0·083	0·492	syst.−109·3=0·49 (ht.−143·8)
13·5	118	+0·483±0·092	0·852	syst.−113·5=0·85 (ht.−150·5)
14·5	880	+0·309±0·033	0·469	syst.−118·4=0·47 (ht.−156·5)
15·5	82	+0·444±0·11	0·715	syst.−119·1=0·71 (ht.−162·8)

Systolic blood pressure as calculated from regression equation

Central Age	**11·5**	**12·5**	**13·5**	**14·5**	**15·5**
Systolic B.P. :—	0·43×ht.+48·2 ;	0·49×ht.+38·7 ;	0·85×ht.−14·5 ;	0·47×ht.+44·8 ;	0·71×ht.+3·5
With each cm. rise in height systolic B.P. rises by	0·43 mm.	0·49 mm.	0·85 mm.	0·47 mm.	0·71 mm.

TABLE 8

EXPECTED SYSTOLIC BLOOD PRESSURE CALCULATED FROM THE REGRESSION EQUATION BLOOD PRESSURE AND WEIGHT

	Weight (kg.)									
Age	25	30	35	40	45	50	55	60	65	70
11·5	102·9	105·7	108·5	111·3	114·1	116·9	119·7			
12·5	100·4	104·3	108·2	112·1	116·0	119·9	123·8			
13·5	98·6	103·0	107·5	111·9	116·4	120·8	125·3	129·7	134·2	
14·5		108·4	111·4	114·4	117·4	120·4	123·4	126·4	129·4	135·4
15·5		107·7	110·2	112·7	115·2	117·7	120·2	122·7	125·2	127·7

of the indices of physique combining both measurements recommends itself. Of the many formulae available the body surface area (B.S.A.) was chosen, not only because of its well known connexion with the basal metabolic rate but mainly for the reason that the size of heart, the stroke volume, as well as the area of the total vascular bed and with it the peripheral resistance, all decisive factors of the arterial B.P., are proportionate to the B.S.A. The body surface area was calculated from DuBois's formula, i.e. B.S.A. $\text{weight}^{0\cdot425}\times\text{height}^{0\cdot725}\times 71\cdot84$ and a chart of the corresponding values is given as Appendix 1.

Table 9 summarizes the correlation between systolic B.P. and B.S.A. The correlation is positive throughout, being highest in the 12·5- and 13·5-year-old boys. The correlation coefficient exceeds in all the examined groups three times its standard error and is therefore significant. The regression coefficient, or in other words, the slope

TABLE 9
CORRELATION OF SYSTOLIC B.P. AND BODY SURFACE AREA

Age	No. of Boys	Mean Systolic B.P.	S.D. Systolic B.P.	Mean B.S.A.	S.D. B.S.A.	Correlation and S.E. of r	Regression Coeff.
11·5	202*	108·1	11·9	1·17	0·09	0·311±0·07	41·1
12·5	117*	109·5	13·3	1·19	0·12	0·419±0·092	46·43
13·5	109*	113·8	13·2	1·32	0·13	0·431±0·096	45·51
14·5	873*	118·0	13·4	1·43	0·17	0·401±0·034	32·56
15·5	82	119·1	15·8	1·55	0·18	0·409±0·11	35·73

REGRESSION EQUATION AND SYSTOLIC B.P. CALCULATED FROM REGRESSION EQUATION

Age	Regression Equation	Systolic B.P.
11·5	systol. B.P.−108·1=41·1 (B.S.A. −1·17)	syst.=41 *B.S.A.+60·1
12·5	syst. B.P.−109·5=46·4 (B.S.A. −1·19)	syst.=46 *B.S.A.+54·3
13·5	syst. B.P.−113·8=45·51 (B.S.A.−1·32)	syst.=45·5 B.S.A.+53·7
14·5	syst. B.P.−118·0=32·56 (B.S.A.−1·43)	syst.=32·6 B.S.A.+71·4
15·5	syst. B.P.−119·1=35·7 (B.S.A.−1·55)	syst.=35·7 B.S.A.+63·7

* Cases of pituitary obesity were excluded as the B.S.A. formula is not applicable in this condition. Therefore means and S.D. differ slightly from the previously given values.

of the line representing the equation, varies but little (Fig. 3) for the various ages. Thus, the association between B.S.A. and B.P. seems to be closer than that of blood pressure and age in the age groups under consideration. This is demonstrated in Table 10 which gives the values of systolic blood pressure as calculated from the regression equation for each year. It will be noted that there is, with the exception of the 15·5-year-group, but little difference in the calculated values of the systolic B.P. for the same B.S.A. in all ages.

For each 0·1 square metre of increase of B.S.A. the systolic blood pressure rises in the following age groups :—

11-year-old by 4·1 mm. Hg
12-year-old by 4·6 mm. Hg
13-year-old by 4·6 mm. Hg
14-year-old by 3·3 mm. Hg
15-year-old by 3·6 mm. Hg

To ascertain whether the assumption is correct that in the age groups concerned the systolic blood pressure is more closely connected with B.S.A. than with the chronological age, 595 boys (excluding

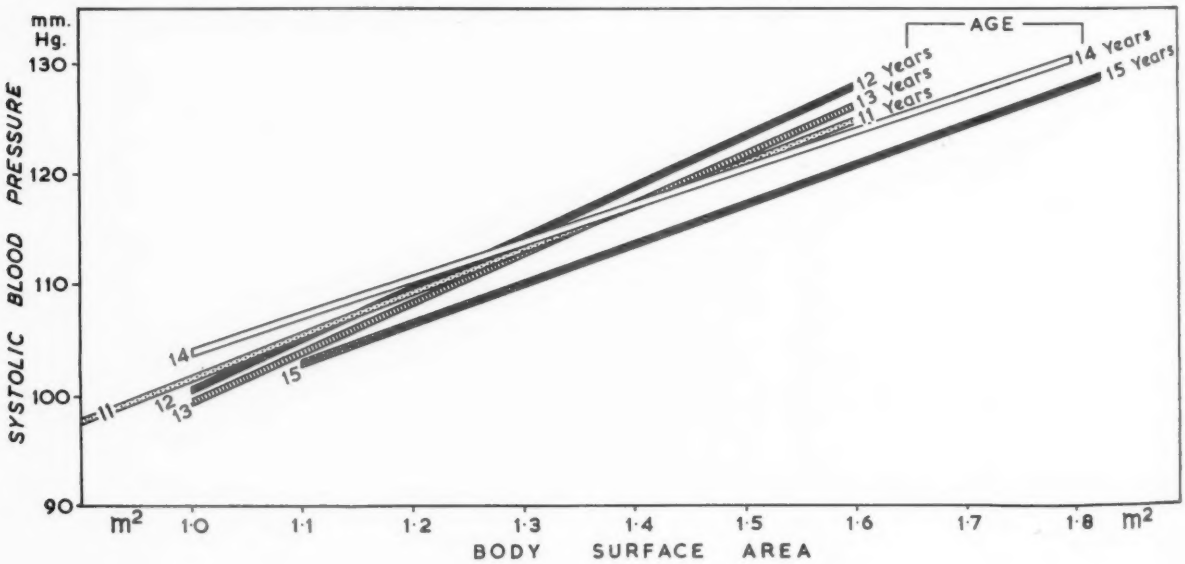

FIG. 3.
Graph representing regression equations blood pressure: body surface are in boys 11, 12, 13, 14 and 15 years of age.

TABLE 10

VALUES OF SYSTOLIC B.P. CALCULATED FROM THE REGRESSION EQUATION B.P. AND B.S.A.

Age	Body Surface Area										
	0·9	1·0	1·1	1·2	1·3	1·4	1·5	1·6	1·7	1·8	1·9m²
11·5	97·1	101·2	105·3	109·4	113·5	117·6	121·7				
12·5		100·7	105·3	109·9	114·5	119·1	123·7	128·3			
13·5		99·2	103·8	108·4	113·0	117·6	122·2	126·8	131·4		
14·5		104·0	107·3	110·6	113·9	117·2	120·5	123·8	127·1	130·4	133·7
15·5			103·0	106·6	110·2	113·8	117·4	121·0	124·6	128·2	131·8

cases of pituitary obesity) between 11 and 14 years were collected, 175 were 11·5 years old; 117, 12·5 years old; 109, 13·5 years old and 194, 14·5 years old. Their systolic B.P. values were plotted against their B.S.A. irrespectively of age. Only the class intervals 0·9, 1·7 and 1·8 m² were omitted since the number of observations was too small. The means of the actual blood pressure observations for each class of 0·5m² are shown as circles in Fig. 4 and the line in the graph represents the regression equation for the whole series: B.P.−112·7=35·8 (B.S.A.−1·29) or B.P.=35·8 B.S.A.+66·5. These means lie approximately on a straight line.

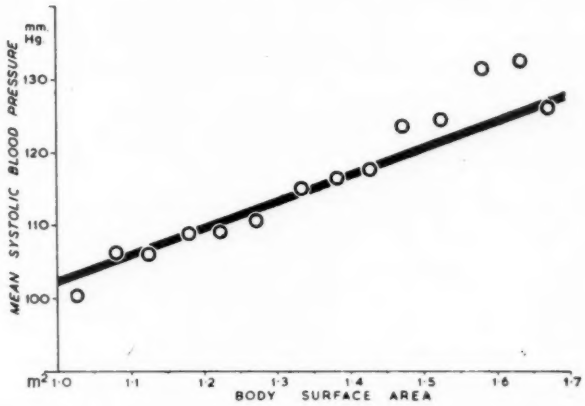

FIG. 4.—Regression equation blood pressure: body surface area in 595 boys 11-14 years of age and observed means of systolic blood pressure. Line represents regression equation: B.P.−112·7=35·8 (B.S.A.−1·29). The groups 1·7 and 1·75 m² are excluded because of their small number.

Conclusions

'Growth', as Washburn (1950) writes, 'does cover a multitude of phenomena but there is a unity which binds them together. As we observe it in a growing child it does include increase in height, in weight, in size of organs; it also includes increasing functional facilities and powers of adaptation to varied environmental influences.' The findings of my statistical study show that arterial blood pressure during puberty in boys follows the laws of growth at this third period of acceleration of growth. At about 13·5 years the average boy spurts in his blood pressure as he does in his height, weight and surface area as well as in the size of heart. But, as in all the last mentioned items, the range of variation in individual values is so wide that mean, median and mode do not provide the answer to the question as to whether the B.P. in a given boy is normal or abnormal. A systolic B.P. of 120 mm. Hg in a 14-year-old boy can mean 'normo-', hyper- or hypotension according to his respective physique, and even a B.P. of 135/85 might be normal for a 14-year-old boy if warranted by his physique. Only by correlating B.P. and body measurements can an approach be sought to establish values of individual normality. Whether the correlation existing between B.P. weight, height and body surface area represents facts of coordination, all of them due to the impact of somatotropic and adrenocorticotropic hormones released by the anterior lobe of the pituitary to an increased extent during puberty, or whether the arterial B.P. just obeys the functional demands of the growing organism remains a question that is outside this survey.

The formulae given in this paper are proposed to enable us to estimate the normality or abnormality of B.P. values in a given individual belonging to the age groups under consideration.

Summary

A study of the blood pressure in 1,417 schoolboys aged 11 to 15 years is presented.

Mean, standard deviation, range and percentage distribution of systolic and diastolic blood pressure were determined, the correlation between systolic and diastolic blood pressure ascertained, and formulae established from the regression equations.

The correlation of systolic blood pressure, weight, height and body surface area was analysed and formulae given for the determination of the normal individual blood pressure, using the regression equations.

The study reveals (1) that there is a wide variation of systolic and diastolic blood pressure which becomes more marked once puberty starts. (2) Systolic and diastolic blood pressure 'spurts' with the beginning of puberty, i.e. at the same time as the third period of acceleration of growth. (3) Of the 11·5-year-old boys 78·1%, and 70·5% of the 12·5-year-old boys have a systolic blood pressure between 90 and 119 mm., whereas three-quarters of the 13·5- to 15·5-year-old boys exhibit a systolic blood pressure between 100 and 129 mm. Of the 15·5-year-old boys, 62·3% have a systolic blood pressure between 110 and 139 mm. About three-quarters of the 11-, 12- and 13-year-old boys have a diastolic blood pressure between 50 and 69 mm. Hg, whereas 72·5 and 81·8% of the 14- and 15-year-old boys show a diastolic blood pressure within the range of 60-79 mm. Hg. There is a statistically significant correlation between systolic and diastolic blood pressure.

To ascertain what might be considered the individual normal blood pressure the correlation between blood pressure and anthropometric measurements was determined. It is positive for weight, height and body surface area, being closer with weight and body area than with height. The association between blood pressure and growth is higher than that of blood pressure and age for the age groups under consideration. Generally each boy has the blood pressure of his physiological age.

The correlation of blood pressure, weight and body surface area permits the prediction of the normal blood pressure for the individual from the respective regression equation, and formulae to this effect are presented.

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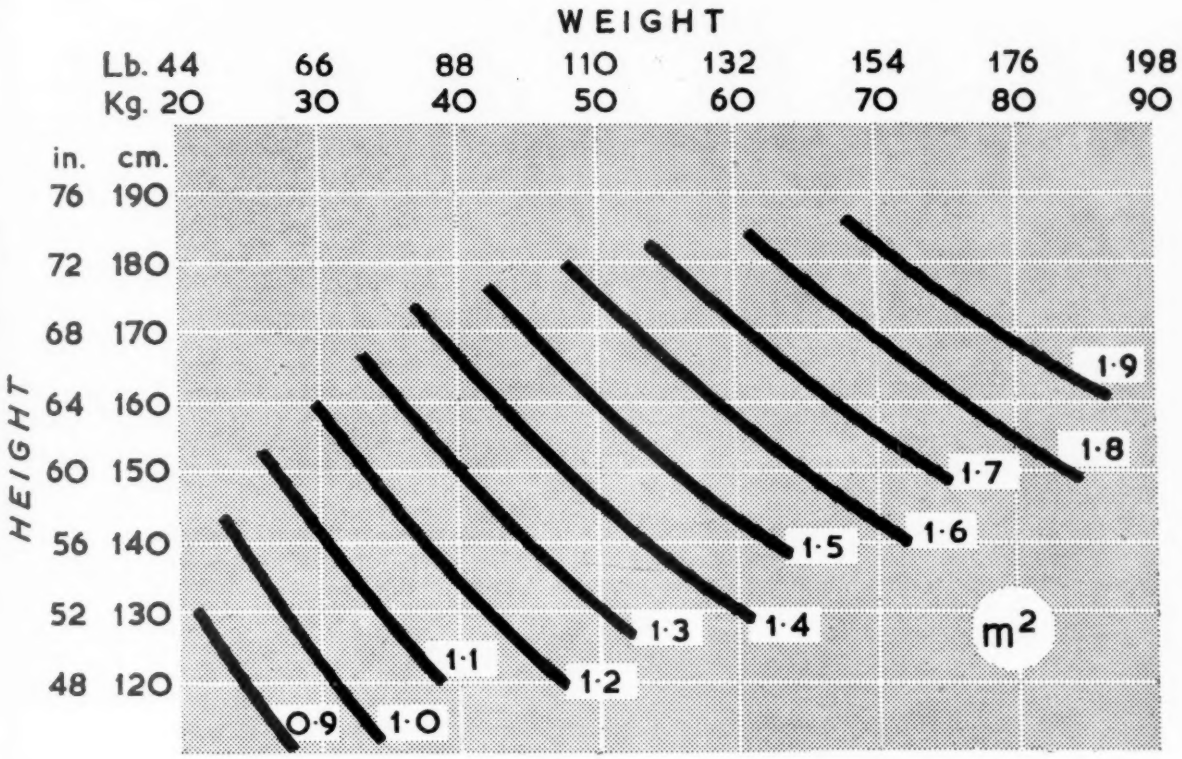
APPENDIX



Graph for the determination of body surface area applying Dr. Bois's formula (B.S.A. = weight (kg.) $0 \cdot 425 \times$ height (cm.) $0 \cdot 725 \times 71 \cdot 84$)

UNILATERAL LIMB LENGTHENING ASSOCIATED WITH HAEMATOGENOUS OSTEITIS IN CHILDHOOD

BY

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(RECEIVED FOR PUBLICATION MAY 2, 1951)

Increase in girth of a long bone following pyogenic inflammation is well known, but there is little recent literature describing increase in length following prolonged bone infection. In a recent series of 100 cases of acute haematogenous osteitis treated with penicillin the disease affected a long bone on 84 occasions. Measurable increase in length of the affected limb occurred in 20 cases. During the same five-year period increase in length of the lower limb was also noted in conditions other than pyogenic bone infection.

The effects of alteration in circulation on bone growth have interested many observers. In the sixteenth century Ambroise Paré noted that stasis hyperaemia stimulated bone growth, and he employed hyperaemia to stimulate callus formation in fractures. Three centuries later Thomas (1886) rediscovered the value of venous stasis in fractures with retarded callus formation. Stanley (1849), Paget (1853) and Bergmann (1868) showed that any long-continued inflammatory process would be followed by increase in length and girth of the bones. Bier (1905) referred to the effects of stasis hyperaemia on bone growth and his book furnishes an excellent historical review of this subject. In recent works on bone disease and fractures there is little reference to increase in length of a long bone produced by circulatory derangement.

Although limb lengthening is most commonly a sequel to haematogenous osteitis, increase in length of the lower limb was noted in the following conditions seen in one unit of the Royal Hospital for Sick Children, Glasgow, during the past five years: (1) 2 cm. lengthening after simple transverse fracture of the femur; (2) 3 cm. lengthening associated with a diffuse angiomatous condition of one leg (congenital arteriovenous fistulae); (3) 2 cm. lengthening after recurrent haemarthrosis of one knee in a child suffering from haemophilia; (4) 2·5 cm. lengthening after severe lacerations of the thigh and calf; (5) 2·5 cm. lengthening in a child suffering from synovial tuberculosis of the hip; and (6) 3 cm. lengthening associated with congenital neurofibromatosis (biopsy revealed plexiform dilatation of veins). In all these conditions there is a common factor of increased blood supply. Leriche and Policard (1926) have suggested an indirect vascular effect on bone growth by the sympathetic nervous system. We have found an increase in length of one lower limb of at least 1 cm. following unilateral lumbar ganglionectomy performed for various conditions.

Before the introduction of penicillin in the treatment of osteitis gross limb lengthening was common and was due to the continuing hyperaemia caused by the presence of an infected sequestrum. Although sequestrum formation was much less common in the penicillin-treated cases, it still occurred (Dennison, 1948) and Figs. 1 and 2 show examples of the resultant increase in length of the affected limb. Where only one of two paired bones was diseased, the increase in length affected both bones equally (Figs. 3 and 4). The hyperaemia presumably affects the soft tissues and increases the blood supply throughout the segment. Irregular growth occurred when there was damage to one part of the epiphysis (Figs. 9 and 10). The increase in length varied from 1 to 3 cm. and the lengthening usually became obvious eight to 12 months after the onset of the disease. The patients were all under 13 years of age at the time of onset of the bone infection.

Sterile sequestra are usually absorbed (Bancroft, 1921) but an infected sequestrum unless extruded must be removed surgically. In 25 successive sequestrectomies performed during the past five years, coagulase positive staphylococci have been grown from either the sequestrum or the surrounding granulation tissue in 24 cases. Advantage of this knowledge was taken in one case in the penicillin-treated series. Pathological fracture of the upper and lower ends of the femur complicating severe bipolar osteitis was followed by 1 cm. shortening of the affected leg (Fig. 5). Radiography revealed a cavity with sequestrum formation, and at operation

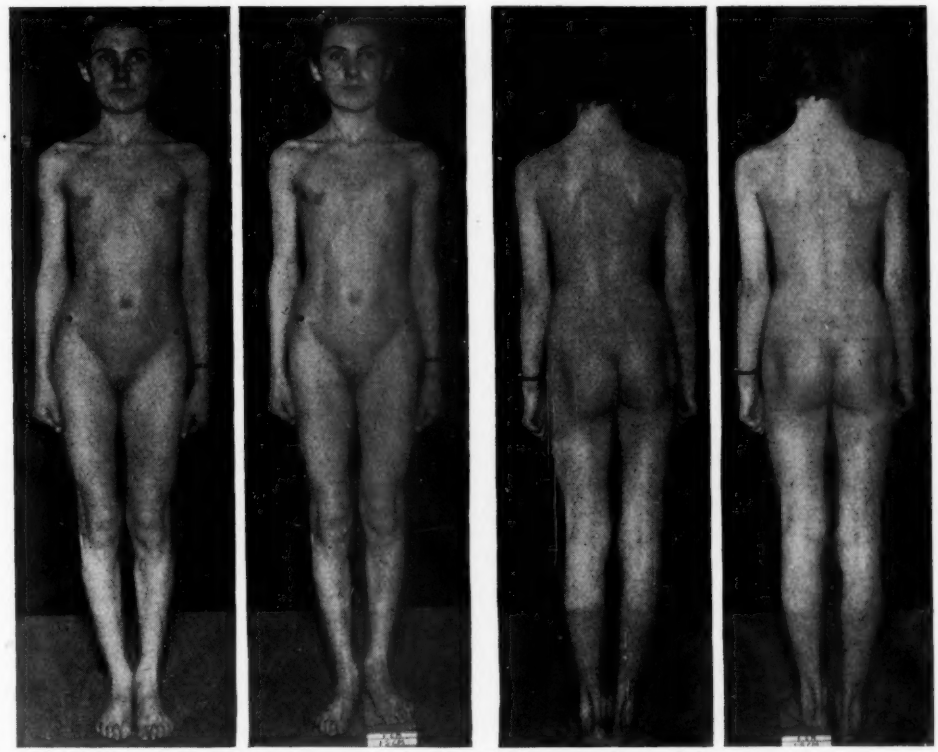

FIG. 1.—Case S.E. Osteitis of right femur. Photographs show 2·5 cm. increase in length of right leg with pelvic tilt, corrected by 2·5 cm. block under foot on sound side.

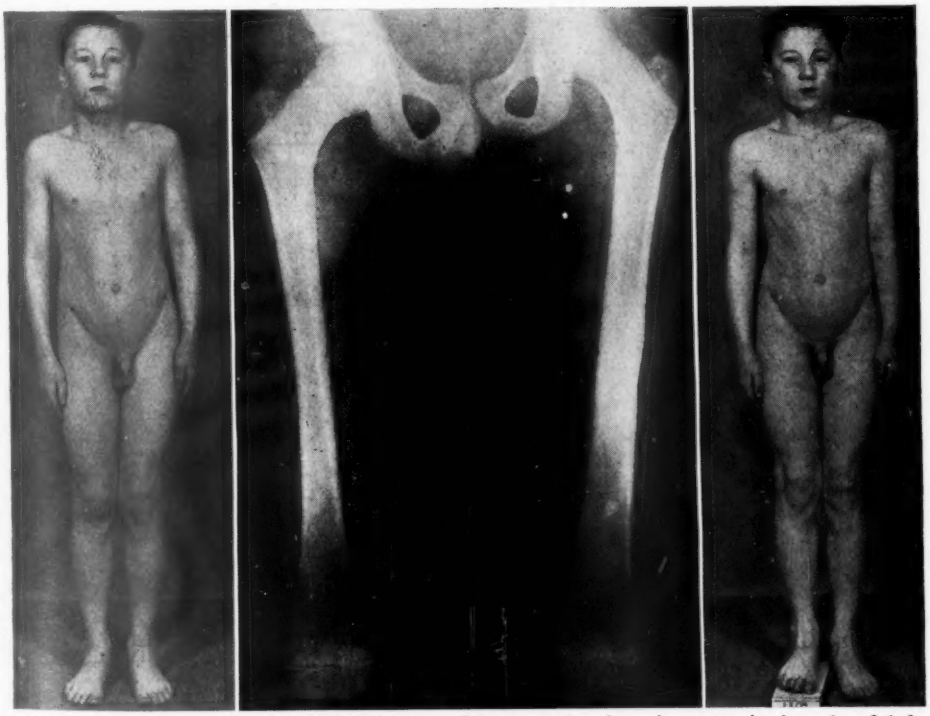

FIG. 2.—Case J.H. Osteitis of left femur. Photographs show increase in length of left leg and pelvic tilt, corrected by 2 cm. block under foot on sound side. X-ray film shows increase in length and girth of left femur.

FIG. 3.

FIG. 3.—Case J.G. Osteitis of right tibia. Radiograph of both tibiae on one film, 18 months after onset of acute osteitis, showing sclerosis of right tibia and increase in length of both right tibia and fibula.

FIG. 4.

FIG. 4.—Case M. McH. Osteitis of ulna. Radiograph film of both forearms, showing increase in girth of right ulna and increase in length of right ulna and radius, two years after onset of acute osteitis.

FIG. 5.—Case M.H. Photographs show shortening of left leg and slight pelvic tilt corrected by 1 cm. block under left foot. X-ray film shows coxa vara following pathological fracture of the neck of the left femur, sclerosis of the shaft and cavitation in lower quarter.

FIG. 6.—Case M.H. (eight months later). Legs of equal length in photograph and x-ray film.

FIG. 7.—Case J.P. Osteitis of right femur. Four years after onset. Photographs show scoliosis and genu valgum partially corrected by 2 cm. block under foot on normal side. X-ray film shows sclerosis and increase in length and girth of right femur.

FIG. 8.—Case L. McI. Osteitis of right femur. Photographs show genu valgum following overgrowth of right femur. X-ray film shows sclerosis and increase in girth and length of right femur.

on February 12, 1949, three small infected sequestra were removed. A fourth sequestrum was deliberately left *in situ* to promote bone growth. On October 4 the remaining sequestrum was removed and Fig. 5 (October 16) shows both legs of equal length.

The growth stimulus over-activated by the increased blood supply gradually passes off and in the actively growing child a moderate increase in length (up to 2 cm.) is rectified within five years. In a series of cases of osteitis treated before the introduction of chemotherapy and followed up until adult life (10-15 years later) an increase in length of 3 cm. noted between 1936 and 1940 was no longer present in 1950. Presumably growth ceases earlier in the overgrown limb.

It must be remembered that the growing child can compensate for a long lower limb by such postural defects as scoliosis (Fig. 7) and genu valgum (Fig. 8). Constant watch must be kept on the patient as such deformities develop insidiously over a period of years if suitable raising is not applied to the footwear of the normal leg.

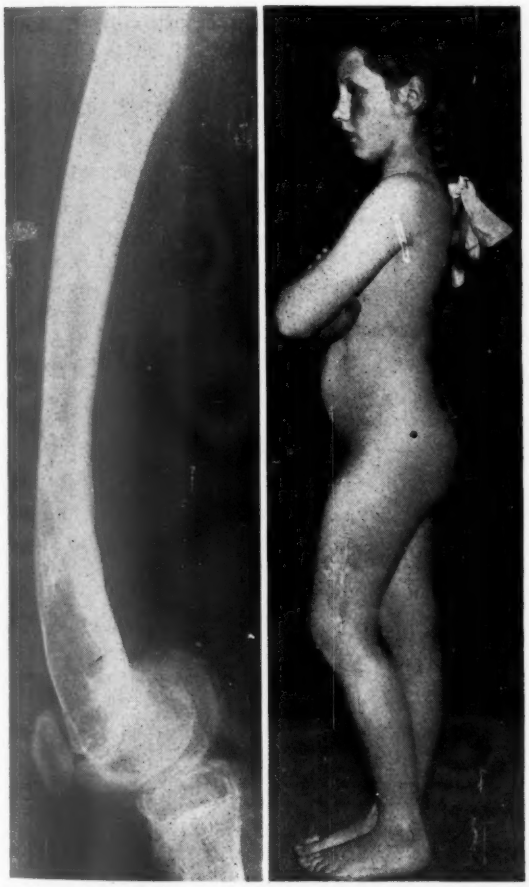

FIG. 9.—Case B.M. Osteitis of left femur. Flexion deformity following damage to lower femoral epiphysis.

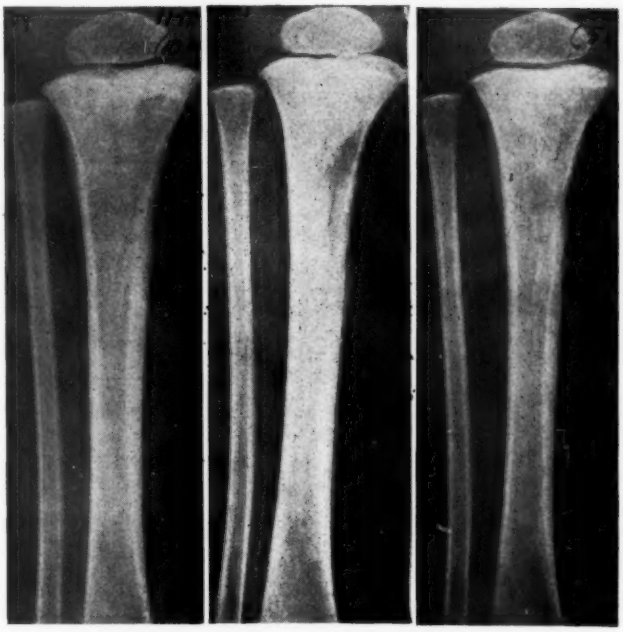

FIG. 10.—Case K.M. Osteitis of right tibia (*b*) two weeks after onset; (*c*) five weeks after onset; (*a*) seven months after onset, overgrowth of medial tibial condyle causing genu valgum.

Summary

In 100 cases of acute haematogenous osteitis the disease affected a long bone on 84 occasions. Measurable increase in length of the affected limb occurred in 20 cases.

Limb lengthening occurs in other conditions in which there is an increased blood supply to the part. Examples of such conditions are mentioned.

Unless appropriate action is taken secondary postural deformities may follow increase in length of one lower limb.

The cases were all studied in Mr. White's surgical wards and I am grateful to him for his helpful advice and criticism. I wish to thank Mr. J. L. A. Evatt, A.R.P.S., medical photographer, Royal Hospital for Sick Children, Glasgow, for the photographs and reproductions of x-ray films.

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A METHOD OF ASSESSING MATERNAL EFFICIENCY FOR SOCIO-MEDICAL SURVEYS

BY

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From the Institute of Social Medicine, Oxford

(RECEIVED FOR PUBLICATION JUNE 13, 1951)

In discussing the importance of the home and social environment to the health of the child, Burn (1947) said:

> 'If I were to ask what each one of us meant by "environment" in respect of child life, I think I know the mental picture which would be conjured up—that of house and district in which the child lived, the state of the backyard and lavatory, the degree of atmospheric pollution of the air he breathed, the purity of the water and the milk he drank, the sanitation of the school premises, etc., etc. This is the truth, but not the whole truth. Environment, defined by the dictionary as "that which surrounds" includes social and psychological influences, which though as intangible and imponderable as air, are nevertheless of decisive importance. It is almost true to say that the infant's environment is his mother.'

The suggestion that the standard of maternal care might be of greater importance to the health and welfare of the young child than any other single influence was strongly advanced by Paton and Findlay (1926). Much valuable data on infant mortality, which support the same suggestion, were put forward by Elderton (1925, 1928). Paton and Findlay were the first to attempt an explicit assessment of this standard.

> 'The factor of maternal character or efficiency is extraordinarily difficult to define and difficult to assess, but a worker of experience is able to classify mothers in this respect into good, bad and indifferent. When the children are repeatedly found to be dirty or verminous, badly clothed and left in bed until all hours of the day, when the house is constantly dirty and uncared for, the mother, without doubt, is inefficient.'

It is the purpose of the present paper to indicate how a reliable assessment of maternal efficiency may be made, to put forward methods whereby a mother may be assigned a numerical score to represent the 'intangible and imponderable', and to give three examples showing how maternal efficiency is associated with the health and environment of the infant.

Qualitative Assessments

It is evident that the definition and assessment of maternal efficiency must rest ultimately upon a subjective basis, and it may be suggested that such an assessment has limited scientific value. Yates (1949) makes the following comments.

> 'Physical measurements are more objective, but qualitative observations are often more capable of summing up the salient features of a complex situation. Thus a qualitative grading by the investigator of the degree of dampness of a house is likely to be more effective than any physical measurements designed to determine the degree of dampness. Moreover by proper standardization and calibration among investigators qualitative observations can themselves be made objective.'

The last sentence represents the crux of the problem. The fundamental uncertainty in any subjective assessment is that another person, or the same person on a different occasion, may make a different evaluation. The more this uncertainty can be reduced, the greater will be the scientific value of the assessment. In this connexion it is worth noting that the particular relevance of such an assessment is in relation to the survey of which it forms a part, and so it is necessary primarily to achieve consistent standards within that survey. If the method derived can also ensure consistent results from one survey to another, so much the better, but this is a secondary consideration.

Although it is difficult to maintain a consistent standard in assessing qualitative factors, the following recommendations may be made. (1) The quality which is to be assessed should be clearly defined. (2) Where possible, several tangible manifestations

of the quality should be appraised, in preference to the quality itself. (3) The various categories should be clearly defined, so as to differentiate between borderline cases, which always present special difficulties. (4) The number of people compiling the records should be kept to an absolute minimum. If more than one person is needed there must be frequent consultation between them, and cross-checking, particularly for borderline cases. (5) For preference the assessments should be based upon several independent observations during the survey period. It is upon these lines that we have attempted to grade the mother's efficiency.

A Method of Assessing Maternal Efficiency

We have continued to use the term 'maternal efficiency', which was introduced by Paton and Findlay, defining this quality as the ability of a mother to cope with and care for her child, and interpreting 'ability' in terms of achievement, not in terms of potentiality. We were concerned to discover the factors which influence the health and development of the child, and so it was the care which the child actually received which was studied rather than the imprecise concept of the mother's basic capacity to manage.

The purposes and methods of the Child Health Survey, which was begun by the Institute of Social Medicine, Oxford, in 1944, have already been outlined (Ryle, 1948; Thwaites, 1950). From the outset it was agreed that an assessment of maternal efficiency was fundamental, and much discussion was devoted to the best method of making it. A survey of the literature and consultations with interested persons in this country suggested that any assessment should be based at least upon the following five factors, which are either indicative of, or (in the case of health) contribute towards, the mother's achievement for her child: state of child, diet of child, attitude of mother to child, state of home and health of mother.

It was therefore decided to class each mother as 'good', 'fair' or 'poor' on each of these counts from observations made during three visits to the home (not more than one of these being by appointment) during the first year of the child's life. Similar assessments have been made each year until the child attained the age of 5 or resigned from the survey. This paper is based upon assessments covering the first year of life of 580 Oxford babies.

After a certain time, it was possible for the one observer* to know from experience what each category meant. Though it is by no means easy to frame working definitions, the following attempt has been made.

Working Definitions for the Assessments

State of Child. This was classified as good, fair or poor.

GOOD. If the child itself was clean and had clean and adequate clothing. It was still considered to be good if a child at the crawling stage had 'top dirt' only, provided that the child had been clean on previous visits; due allowance was also made for 'play dirt' in the older age groups.

FAIR. If the child was dirty or else had dirty clothing, the latter being more usual. This assessment was made if a child of 6 weeks had dirty nails, but not if a child, who had previously been clean, was found to have dirty nails during the crawling period.

POOR. If ingrained dirt and dirty clothing were found on each occasion.

When in doubt, the lower assessment has been recorded. No child was marked down for pediculosis capitis *per se*. However, with one exception, the children who were independently noted at the clinical examinations as having pediculi, had come from dirty homes.

Diet of Child. This was classified as good, fair. or poor.

GOOD. If the diet was adequate in amount and kind, and given at reasonably regular intervals. If an infant was not receiving regular vitamin supplements, it was verified that he was getting these in natural foods.

FAIR. If there was evidence of any one of the following: gross overfeeding or underfeeding; complete disregard of any timing; diet inadequate in vitamins or any other essential constituent.

POOR. If marked down on two or more of the above points; and if no care was taken at all, e.g. perpetual bread and margarine.

Again the principle of marking down the borderline assessments has been observed. This was expedient since the general level of nutrition was high, but it is realized that it may not be generally applicable. Some salutary observations are made in the report of the United Nations Food and Agricultural Organization on *Dietary Surveys: Their Technique and Interpretation* (Norris, 1949).

Attitude of Mother to Child. This assessment was considered essential in order to differentiate the efficient mother from the efficient housewife. The needs for the mental welfare of the child, as set forth by Anderson (1948) may be grouped as follows: (1) security; (2) discipline and habit training;

* For the period October, 1944, to June, 1946, the social reporting was in the hands of Miss Elisabeth J. Williams. After a month of joint work, the reporting has been the sole responsibility of one of the writers (E.J.T.).

(3) love and affection (' wantedness '); (4) equality with and ' sameness ' to others; (5) opportunity and space to indulge in noisy, active play, possessions.

The attitude of the mother was classified as good, fair or poor.

GOOD. If all these five needs were apparently being met.

FAIR. If one or two appeared to be lacking.

POOR. If three or more of the above were lacking.

Whereas the other assessments have been down-graded in borderline cases, the mother was always given the benefit of any doubt in this instance. In order to guard against possible errors of judgment due to personal bias, the opinions of other workers, such as health visitors, almoners and the super-intendents of the day nurseries, were sought as a reinforcement where this was felt to be necessary.

State of Home. This was classified as good, fair or poor.

GOOD. When the home was clean and reasonably tidy. If the mother was house-proud to the extent of unduly limiting active play she was marked down on the assessment of ' attitude ', though not, of course, on the assessment of ' state of home '.

FAIR. When the home was fairly clean: the intermediate grade.

POOR. When the house was dirty and smelly, and no attempt was made at housework; for instance if food was permanently on the table and beds never made.

Though the first visit might be by appointment, the majority of visits were unexpected. The kitchen and bedrooms were usually seen at least once, and the other rooms on several occasions and at different times of the day. Every attempt was made to prevent first impressions colouring the picture; for instance a new ' prefab.' *looked* so much cleaner than one of the older houses with shabby Victorian furniture, but might well not be so. The lower assessment has been recorded where there was uncertainty.

Health of Mother. This was classified as good, fair or poor.

GOOD. If the mother was in good health and able to continue normal household duties. If a mother became pregnant again, and said she felt well, or if she had not more than two weeks' illness (for instance one or two colds) she was still placed in this category.

FAIR. This assessment included the mother who had (1) from two to four weeks' illness, but who was otherwise able to continue normal duties; (2) chronic complaints, e.g. controlled diabetes, ' nerves ', deafness; (3) minor gynaecological complaints, anaemia; (4) residual paralysis, necessitating the use of a caliper, or orthopaedic complaints.

POOR. If the mother's function as a housewife was interfered with by serious complaints, such as (1) rheumatism with heart involvement; (2) thyrotoxicosis involving hospital treatment or operation; (3) tuberculosis, under treatment; (4) blindness within the meaning of the Blind Persons Act (1920).

Though the clinician who saw the children was available for consultation, the recorded assessment was based on the mother's description. Known borderline cases have been down-graded but it is possible that health has not been scaled down often enough. For instance, after frequent pregnancies, some mothers had probably not been fighting fit for years, and so had no criterion of health, although they said they had ' no complaints '. A standard comment of the mothers was ' I *have* to keep well '.

A Method of Deriving a Score for Maternal Efficiency

When the five assessments had been made, there arose the problem of combining them into a single measure. Unless each was taken to be of equal value as an indicator of maternal efficiency some decision was necessary as to their relative importance. There was little unanimity in the views of those whom the Institute consulted on this topic, and so it was resolved to use a statistical approach known as factor analysis (Holzinger and Harman, 1941). In this approach the data themselves determine what score should be given to each of the five factors. Each of the assessments was regarded as a more or less close measure of the underlying concept of maternal efficiency. The fundamental assumption was then made that the assessments which were most closely related to each other were also most closely related to the underlying concept. From calculations based on the interrelations of the five assessments, each was assigned a score, which was indicative of the closeness of the association between it and the underlying concept.

Details of Computation. The particular technique used was the method of principal factors. The first principal factor only was calculated, and taken to be that of ' maternal efficiency '. One of us (E. J. T.) felt that there was a greater gulf between the ' poor ' and ' fair ' grades than between ' fair ' and ' good '. Hence the correlation between each pair of assessments was estimated from a formal calculation with working units of 1, 0 and −2 assigned arbitrarily to the good, fair and poor grades respectively. The calculations were

made on the 580 sets of five assessments, and the correlation coefficients found were as follows:

	Diet of Child	Attitude of Mother	State of Home	Health of Mother
State of child ..	0·565	0·606	0·706	0·243
Diet of child ..		0·555	0·560	0·285
Attitude of mother			0·497	0·256
State of home ..				0·223

The communalities needed for the analysis were estimated from the averages of all triads.

Scores. The following system of scores resulted from the analysis, giving a possible maximum of 100. Since it was felt that there was a greater gulf between the 'poor' and 'fair' grades than between 'fair' and 'good', this was made a feature of the system of scores, by giving the 'fair' grade two-thirds of the scores for the 'good' grade.

	Good	Fair	Poor
State of child	32	22	0
Diet of child	25	16	0
Attitude of mother ..	19	13	0
State of home	19	13	0
Health of mother ..	5	3	0

The order of importance assigned to the five factors by the analysis is the order in which for convenience they have already been considered in this study.

As a matter of interest, E.J.T., having no knowledge of the results of this analysis by I.S., was invited to assign scores, totalling to 20, to the five factors to represent what she considered to be their relative importance as measures of maternal efficiency. Her scores were as follows:

	E.J.T.	Factor Analysis
State of child	6	6
Diet of child	5	5
Attitude of mother ..	3	4
State of home	4	4
Health of mother ..	2	1

The correspondence is very close. Although it would be unwise to make too much of it, the result certainly suggests that factor analysis is a realistic technique to apply to this problem.

Scores for Maternal Efficiency

Table 1 shows how many of the 580 mothers were classified as good, fair or poor on each of the five counts. It is clear that the general level of mothercraft was high, since the majority of the mothers were graded 'good' and very few were classed as 'poor'. It was expected when the Child Health Survey started that this would be so for a group of volunteers living in Oxford. This raises the question whether more stringent criteria should have been used in order to yield a more balanced classification. This was deliberately not done because it would have given undue prominence to the social worker's personal opinions of what was desirable and what was undesirable in the child's environment.

TABLE 1

CLASSIFICATION OF 580 MOTHERS ACCORDING TO FIVE INDICES OF MATERNAL EFFICIENCY

	Good	Fair	Poor	Total
State of child ..	476	97	7	580
Diet of child ..	503	75	2	580
Attitude of mother to child ..	466	109	5	580
State of home ..	418	137	25	580
Health of mother	457	120	3	580

Table 2 shows the maternal efficiency scores derived from the five indices. No fewer than 320 mothers (55·2%) were classed as 'good' on all five and so score 100. A further 50 (8·6%) were only marked down by two points on account of fair health. At the other end of the scale were 49 mothers who scored less than 70. The lowest score recorded was 3 for a mother who had fair health, but was otherwise graded poor. These figures again bring out the high standards in the group under survey.

TABLE 2

CLASSIFICATION OF 580 MOTHERS ACCORDING TO SCORES FOR MATERNAL EFFICIENCY BASED UPON FIVE ASSESSMENTS

Score*	Number of Mothers	Percentage
100 ..	320 } 370	55·2 } 63·8
98 ..	50 }	8·6 }
90–95 ..	78	13·4
80–89 ..	51	8·8
70–79 ..	32	5·5
Under 70	49	8·4
	580	99·9

* By factor analysis.

Choice of Methods for Assessing and Scoring Maternal Efficiency

At this point it was necessary to consider whether the procedures originally decided upon, and outlined above, for grading maternal efficiency should

be modified in the light of experience. The principal modification concerns maternal health. During the course of the survey, one of us (E.J.T.) became increasingly convinced that ill-health in the mother was frequently overcome and so made little difference to her efficiency; for this reason health should not be used as an indicator of a mother's efficiency. Moreover, health is not, like the other four, a direct measure of the mother's achievement but a measure of her potentiality in relation to the child. The assessment is thus of a different character from the others, and this is one of the reasons why such low scores are allotted to maternal health by the factor analysis. It was therefore decided to omit maternal health from the five assessments and to base the score for maternal efficiency upon the remaining four. This has an added advantage. By using a measure of efficiency which does not incorporate maternal health explicitly it is possible to regard the mother's health and her efficiency as two separate influences upon the health and development of her child, and to decide upon their relative importance.

It was next necessary to consider whether a simpler method of scoring would not be as satisfactory as the complex one already outlined. Whatever method was adopted, all those mothers who were classed as ' good ' on the four assessments of achievement had to score full marks. These numbered 371 (64% of the total). Thus the only difference between alternative methods was the way in which they grouped the remaining 36%; this fact considerably lessened the scope for any variant of method.

The simplest alternative was to give an equal weight to each assessment, say scoring 3 for ' good ', 2 for ' fair ' and 1 for ' poor ' on each. This system was tried out and was found to have a negligible effect on the original grouping. This shows that for the study of mothers whose standards are as high as those of the present series a scoring system based upon factor analysis is unnecessarily elaborate, and gives little extra discrimination between mothers compared with a simple scheme. The approach by factor analysis has been outlined here for two reasons. First, it justifies in this particular instance the use of a simpler scoring system with equal weights for each assessment, a step which would otherwise have appeared arbitrary. Secondly, it illustrates a technique for combining a number of assessments which should be useful in other socio-medical surveys. It has already been used in studies of physical constitution (Burt and Banks, 1947), and the assessment of physical fitness (Cureton, 1947) as well as in its original field of application to psychology.

A number of other methods of scoring were investigated. They all gave similar results, and there was no reason to prefer any of them to the very simple pattern just suggested. Consequently this was adopted for scoring maternal efficiency. Table 3 shows the distribution of the mothers according to this revised score for efficiency.

TABLE 3
CLASSIFICATION OF 580 MOTHERS ACCORDING TO SCORES FOR MATERNAL EFFICIENCY BASED UPON FOUR ASSESSMENTS

Score*	Number of Mothers		Percentage	
12	371		64·0	
11	81		14·0	
10	48		8·3	
9	31		5·3	
8	31		5·3	
7	11		1·9	
6	3	49	0·5	8·4
5	3		0·5	
4	1		0·2	
	580		100·0	

*Score: 3=good, 2=fair, 1=poor.

Maternal Efficiency According to Sharing the Home. As a first example of the use of the maternal efficiency score we decided to see whether it varied if the family unit shared its accommodation with others. The family unit was defined as the survey child, together with any brothers or sisters, and the parents. The figures in Table 4 show that family units living on their own achieved the highest

TABLE 4
MATERNAL EFFICIENCY RELATED TO SHARED ACCOMMODATION

Family Unit	Percentages of Mothers Scoring					Total	No. of Mothers
	12	11	10	9	8 or less		
Living alone	68·3	12·7	7·9	4·0	7·1	100·0	252
Sharing with lodgers ..	63·6	15·5	7·8	7·3	5·8	100·0	79
Sharing with relatives	60·8	12·7	8·9	5·1	12·7	100·2	206
Living in ' rooms ' ..	46·5	16·3	11·6	4·7	20·9	100·0	43
All family units ..	64·0	14·0	8·3	5·3	8·4	100·0	580

TABLE 5

MATERNAL EFFICIENCY RELATED TO NON-SPECIFIC INFECTIONS IN THE CHILD IN THE FIRST YEAR

Number of Non-specific Infections in Child	Percentages of Mothers Scoring					Total	No. of Mothers
	12	11	10	9	8 or less		
0–1	68·8	11·7	9·3	4·9	5·2	99·9	324
2–3	63·5	15·7	4·1	5·6	11·2	100·1	197
4 or more ..	39·0	20·3	16·9	6·8	16·9	99·9	59
All children	64·0	14·0	8·3	5·3	8·4	100·0	580

standards of efficiency; 68% of the mothers scored full marks of 12. The lowest levels of score were among those living in ' rooms ', the corresponding percentage being only 46%.

Maternal Efficiency and Non-specific Infections in the Infant. Table 5 shows that there is a definite relation between maternal efficiency and the number of non-specific infections (colds, etc.) in the first year of life. Where the child had no infections, or only one, nearly seven out of 10 of the mothers scored full marks. Where the child had four or more infections, only four out of 10 mothers scored full marks. Further investigation is of course necessary to decide whether there is any causative connexion between these two factors, or if some other influence, such as crowding, is responsible for the association.

Maternal Efficiency and Gastro-enteritis in the Infant. The third example (Table 6) shows that there was no relationship between maternal efficiency and the liability of the child to contract gastro-enteritis in the first year. The variations between the two lines of percentages could well have arisen by chance. It will, however, be shown in a later report that children are less liable to contract gastro-enteritis while still entirely breast-fed. Since the type of feeding was not included as such in our assessment of maternal efficiency, its influence is not revealed by this index, and will be studied separately.

Summary and Conclusions

Several previous investigators into the problem of child health have stressed the importance of the ' efficiency ' of the mother as an influence upon the health and development of the child. In connexion with its Child Health Survey, the Institute of Social Medicine in Oxford has devised a method of assessing this quality, which is presented in this paper, with examples of its use.

' Maternal efficiency ' is defined as ' the ability of a mother to cope with and care for her child '. Emphasis is laid throughout on assessing the mother's actual achievement in relation to her child, rather than her basic capacity or her intentions.

An index of maternal efficiency was first derived from five separate assessments of the mother and of the environment which she created for the child, these assessments being combined by the statistical technique of factor analysis.

After due consideration of this index it was decided to omit the assessment of maternal health and base a revised index upon four assessments only, namely, the state of the child, the diet of the child, the mother's attitude to the child and the state of the home. The standards of assessment are set out. At the same time it was decided that the technique for combining the assessments was unnecessarily complicated in the present instance, and that it would be a practical advantage to replace it by a much simpler system.

TABLE 6

MATERNAL EFFICIENCY RELATED TO GASTRO-ENTERITIS IN THE CHILD IN THE FIRST YEAR

Gastro-enteritis in Child	Percentages of Mothers Scoring					Total	No. of Mothers
	12	11	10	9	8 or less		
No attack	63·3	14·1	7·6	6·3	8·7	100·0	447
One or more attacks	66·2	13·5	10·5	2·3	7·5	100·0	133
All children	64·0	14·0	8·3	5·3	8·4	100·0	580

Examples are given of the relation between the revised index of maternal efficiency and three aspects of the child's environment and health.

We are much indebted to the late Professor J. A. Ryle and Dr. W. T. Russell, who were responsible for instituting the Child Health Survey and for the basis of this method of assessing maternal efficiency. We should also like to thank Dr. Alice Stewart and Dr. R. W. Parnell for their comments on the draft of this paper.

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THE TRYPTIC ACTIVITY AND PRESENCE OF CORNIFIED SQUAMES IN MECONIUM AS A DIAGNOSTIC AID IN CONGENITAL INTESTINAL OBSTRUCTION

BY

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With the increasing efficiency of the surgery of the newborn the accurate diagnosis of congenital anomalies of the alimentary tract has become more important. The technical aids to the diagnosis of congenital intestinal obstruction are of three types: (1) radiological examination, taking advantage of the gas in the bowel and occasionally using opaque substances; (2) the examination of vomited and aspirated material for the presence of bile and pancreatic ferments; and (3) examination of meconium. Of these methods radiology is undoubtedly the most widely practised, and few clinicians use other tests. However, it is not an infallible guide as can be seen by the figures from the Children's Hospital in Boston in 1946, when only seven of 23 cases of congenital intestinal atresia were correctly diagnosed by radiology. The radiological appearances in intestinal anomalies are well described by Caffey (1950) and by Ladd and Gross (1941) and are not the concern of this paper.

The importance of the examination of vomited material and fluid obtained by gastric suction is obvious. The presence of bile indicates patency of the biliary and gastro-duodenal passages. If duodenal suction is used the findings of tryptic activity in alkaline fluid would suggest an absence of that type of meconium ileus which is usually associated with gross pancreatic change.

The naked eye examination of the stools in intestinal atresia is occasionally misleading. When the stool consists of a pale, mucoid thread or small green-centred fragments covered with mucus-like 'rabbit droppings' there is no confusion (Fig. 1), but not infrequently infants with atresia situated fairly high up in the intestinal tract pass meconium which is described by experienced paediatricians as being normal. It is these apparently normal stools which cause confusion in diagnosis and delay in treatment. This is doubly unfortunate since these high obstructions are most amenable to surgical treatment. In such cases more detailed examination of the meconium can be of assistance.

The test that is most widely known and used in the diagnosis of intestinal atresia was described by Farber in 1933. It depends upon the observation that normal meconium is formed, in part, from amniotic fluid swallowed *in utero*. This was clearly

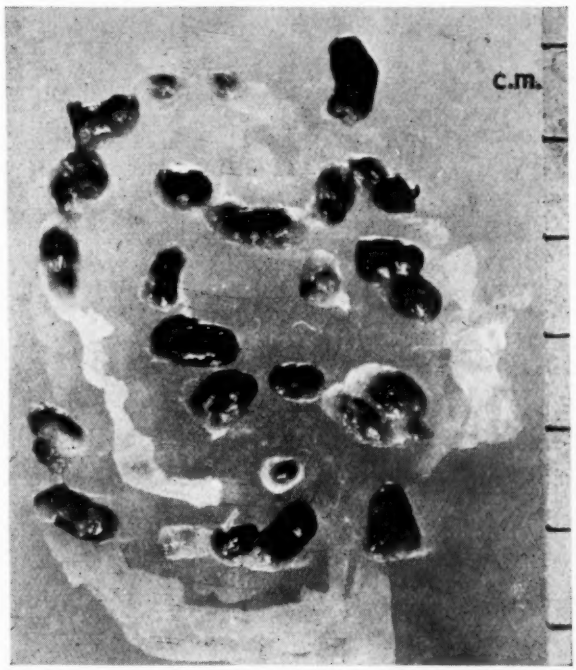

FIG. 1.—Abnormal meconium from a child with intestinal atresia, showing small green fragments, 'rabbit droppings', covered with pale mucus and separated by threads of mucus.

FIG. 2*a*.—Section of skin from newborn child showing cornified epithelial squames flaking off (× 150 Masson's trichrome).

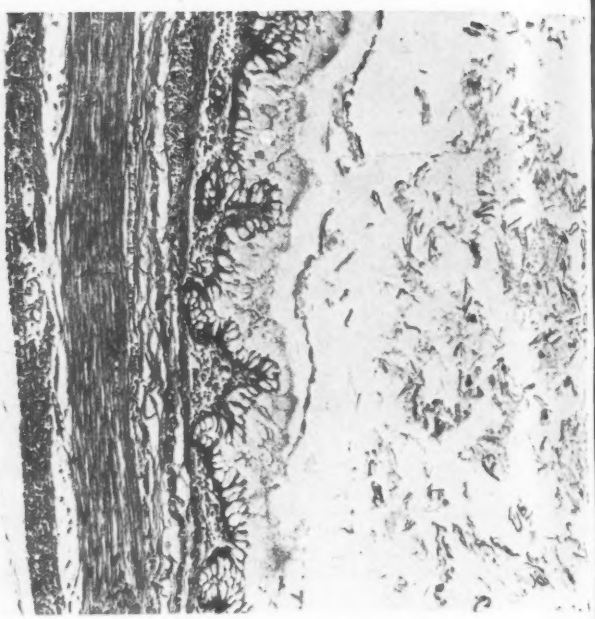

FIG. 2*b*.—Section of gut containing meconium from a newborn child showing the squames in the meconium (× 100 Masson's trichrome).

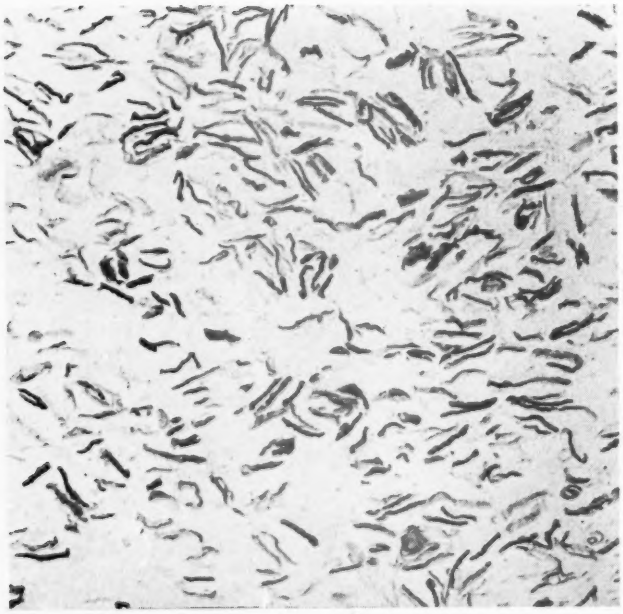

FIG. 2*c*.—Section of meconium showing cornified squames, many in cross section (× 200 Masson's trichrome).

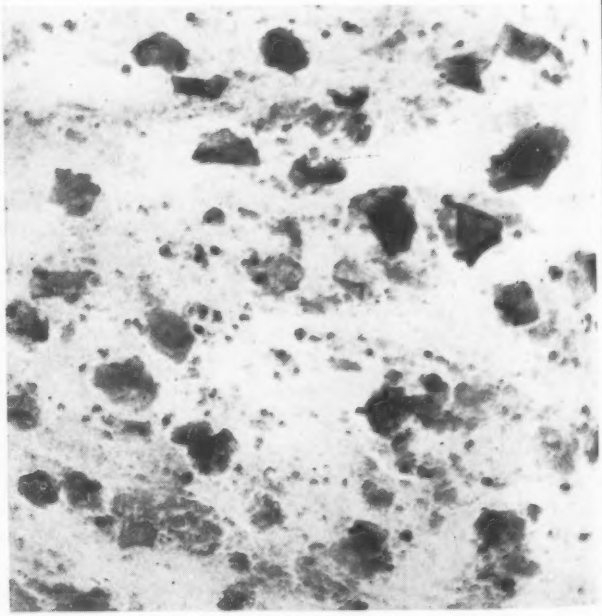

FIG. 2*d*.—Smear of meconium from a normal child showing cornified squames. × 200. (For stain, see Appendix.)

illustrated by Becker, Windle, Barth and Schulz (1940). They injected colloidal thorium hydroxide into the amniotic sacs of guinea-pigs and observed several complete cycles of passage through the intestinal tract in animals that were later born normally. Foetal ingestion and gastric concentration, though not complete intestinal cycles, have also been demonstrated in man. Amniotic fluid contains desquamated cornified epithelial cells and these, since they are not destroyed during passage through the alimentary tract, are normally present in meconium (Fig. 2). In Farber's test these cells are identified by their staining properties (for technical procedure see Appendix). Woody (1947), showing the usefulness of Farber's test, reported correct diagnosis with it in 23 of 24 instances in 1946-47, compared with a correct diagnosis in only seven of 23 cases in the previous nine years when the test was not used. The test is recommended in most of the standard textbooks of paediatrics. There are, however, some sources of error. Errors can occur in staining and in examining the films. Cornified squamous cells are present round the anus and become attached to the surface of the stool as it is passed. Squamous cells may also be introduced into the rectum by the examining finger or into the colon by an attempt at irrigation. For that reason Farber suggests that the meconium of which the film is made be taken from the inside of the meconium stool. The tenacious nature of the meconium makes this operation difficult, hence the finding of a few cornified squamous cells does not theoretically exclude the diagnosis of intestinal atresia.

During a survey in this laboratory of the tryptic activity of stools it was noted that there was tryptic activity in the first meconium stool of many infants, whereas none was found in two cases of meconium ileus and in two cases of intestinal atresia. For that reason a survey of the tryptic activity of meconium was carried out to test its usefulness in neonatal diagnosis, and, at the same time, the value of Farber's test was checked.

Materials and Methods

The first, and in some cases subsequent, specimens of meconium were collected from 100 normal infants born at a municipal maternity hospital. Meconium was also obtained from three cases of meconium ileus and five of intestinal atresia, all cases being confirmed at necropsy or operation.

Meconium was collected by the nursing staff into small waxed containers. These specimens were examined separately for tryptic activity, and in 94 instances Farber's test was also carried out. The slides were examined by me for cornified cells and then sent, as a set of numbered slides, to three pathologists who consented to examine the smears and report on the presence or absence of cornified cells. The pathologists had no knowledge of the children from which the specimens came other than that some were normal and some abnormal, and were unaware of each other's findings. The slides were later decolorized and re-stained by a different method (Appendix), and again examined by other pathologists.

Tryptic activity was measured using a simplified modification of the method described by Andersen and Early (1942) for the examination of duodenal juice (Appendix).

Results

Tryptic Activity. The tryptic activity of 100 first specimens, together with 42 second specimens of meconium from 100 unselected normal infants, is expressed as a distribution curve in Fig. 3.

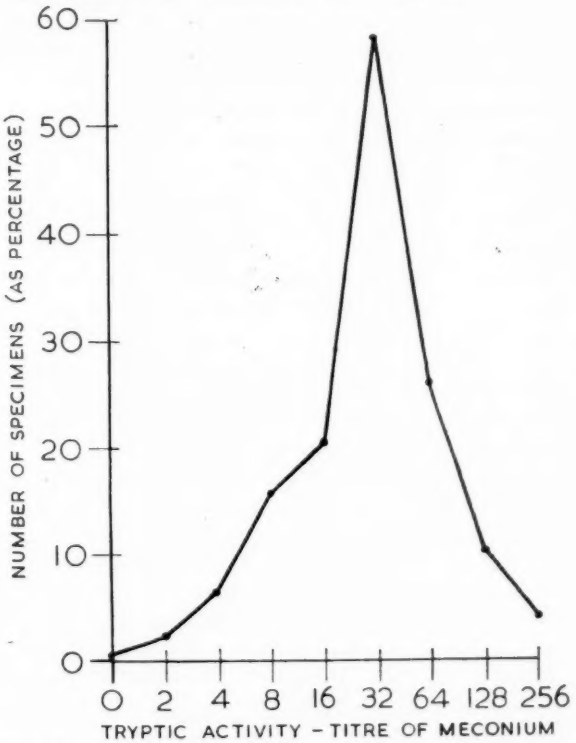

FIG. 3.—Distribution diagram showing the percentage of specimens with tryptic activity at a varying dilution; 142 specimens of meconium from 100 normal newborn children.

Estimations were at first carried out using four tubes only, i.e. to a dilution of 1 in 16 and to a final negative dilution in the last 50 specimens only.

One case showed no tryptic activity. Three out of 142 (2·1%) had activity in only the first dilution; nine (6·3%) to second dilution and 23 (15%) to the third dilution, i.e. one in eight. Fifty-eight out of 142 showed activity to a dilution of 1 in 16, but since

the majority of these had not been tested further only specimens examined to dilutions and showing no activity beyond this dilution were used in the distribution graph. Of the 50 specimens examined to further dilutions, 29 (58%), 13 (26%), five (10%) and two (4%) showed activity to the titre of 1 in 32, 64, 128 and 256 respectively.

We were unable to obtain further specimens from the one case showing no tryptic activity in the first specimen or from two of the three cases showing activity only in the first tube. Further specimens of meconium were available from the third child, and activity was present at a dilution of 1 in 4 when the child was 10 hours old, 1 in 32 at 20 hours and again at 40 hours.

Of the meconium from five cases of intestinal atresia, the material was green in four and showed no tryptic activity. In the fifth case the meconium was grossly abnormal consisting almost entirely of greyish mucus; tryptic activity occurred in the first tube only with this material.

Examination for Cornified Cells. Ninety-six numbered slides of meconium, four from cases of atresia and the rest obtained from normal newborn children, were stained using Farber's technique. The slides were stained to my satisfaction and were then sent to three pathologists who reported on them independently. Their results were: pathologist A, 30 positive, 66 negative; pathologist B, 31 positive, 65 negative; pathologist C, 46 positive, 50 negative. Superficially there appeared to be some agreement, but, when the cases were analysed, it was found that frequently a slide which one had recorded as double positive was regarded as negative by another. In all, 14 slides only were consistently reported as positive and 38 as negative. Of the four smears from cases of atresia, two had consistent negative reports and the other two were reported as positive by at least one pathologist. Thus, of 96 slides the report was consistently correct clinically in only 16 instances. Complaints of the staining method were made by all. The chief complaints were of the variation of stain-retention of the squames, and the absence of stain in the rest of the tissue which made the preparations tiring to look at and difficult to keep in focus. The smears were therefore decolorized and re-stained using part of the usual Masson's trichrome stain (Appendix), as it had been noted that sections of the newborn intestine stained by the latter method showed a brilliant contrast between bright red squames and green background with this method. Squames stained in this way were much more easily identified and were found by my colleagues in all the smears which had previously been found negative.

Large numbers of squames were seen in the majority of the preparations, but in extremely small numbers in a few of the smears from normal meconium. In all of the cases of atresia a few squames were found. It was not found possible to distinguish the few normal smears with very few squames from the smears from the cases of atresia.

Discussion

The object of this study was to investigate the normal variation of tryptic content and cornified squames of meconium and so gauge their value in the diagnosis of atresia. One test depends on the infant swallowing amniotic fluid and the other on the secretion of trypsin by the pancreas. Both depend on the patency of the alimentary tract below the level of the duodenum, but the former also requires patency of the upper alimentary tract. The results show that Farber's test may give results which are misleading and also explain why in some centres the test is found useful, but in many instances only lip service is paid to the test. When examination for cornified squames is carried out by a clinician or general pathologist better results are likely if the smear used is stained with acid fuchsin and with light green as a counterstain instead of using the staining method recommended by Farber. There is no justification for statements such as that recently made by Wyatt (1951): 'If an atresia is present, no meconium shows on the diaper, and the rectal swab gives a negative Farber test. If the condition is stenotic in nature small amounts of meconium are present and Farber's test is positive.' The conclusions that can be drawn from the investigation of Farber's test are that (1) it is not an 'all or none' test, (2) that when Farber's stain is used previous experience of the method makes a great difference to the result obtained, but this difficulty can to a great extent be overcome by using a different staining technique; (3) the failure to find cornified epithelial cells is not proof of atresia; (4) the presence of a few squames is not proof of patency; (5) the test would seem to have definite value in that the finding of many squames is an indication that a lumen is present throughout the alimentary tract.

There are embryological, clinical and pathological considerations in support of the use of tryptic activity as a measure of patency of the lower alimentary tract. There is little doubt that the pancreas secretes before birth; secretory granules are present in the pancreas of the foetus (Keene and Hewer, 1929), and increase greatly just before birth (Werner, 1948). Madey and Dancis (1949) showed that the concentration of proteolytic enzymes from the duodenum of premature infants is similar to that in older children, and Klumpp and Neale (1930)

showed that the proteolytic enzymes in the newborn and the rest of childhood are equal.

The examination of meconium for tryptic activity is similar to the test widely used as an aid to diagnosis in fibrocystic disease of the pancreas (Shwachman, Patterson and Laguna, 1949). The digestion of the gelatine film on an x-ray plate is a suitable method of performing the test, but we have preferred to use a tube method as it is more convenient, and, in this laboratory, the same method is used for duodenal fluid. The test takes altogether about an hour and a half and can be done with the minimum of technical skill.

The range of tryptic activity found in meconium shows the type of distribution usual in physiological material. The results show that in over 90% of instances the normal meconium showed tryptic activity to a dilution of at least 1 in 8. In no case of atresia below the ampulla of Vater has tryptic activity been found with a titre of that degree. In two cases of atresia in which only necropsy material was available tryptic activity was present in the upper dilated segment and absent in the contents of the lower bowel. In a recent case of atresia, which had bile in vomited material and no tryptic activity of the meconium, there was a rapid onset of tryptic activity in the stools when the obstruction was relieved by operation.

Tryptic activity was absent in the meconium in three cases of meconium ileus, a finding to be expected in the type of ileus associated with pancreatic changes described by Farber (1944), but it is to be noted that tryptic activity was present in the faeces of the case of meconium ileus reported by Hinden (1950).

The absence of tryptic activity does not provide us with a certain diagnostic test for atresia. There was one normal infant with no tryptic activity in the first specimen of meconium. This extreme variation of the normal must be remembered.

If there is an atresia above the ampulla, tryptic activity should be present in the meconium and its absence would suggest a second obstruction lower down in the alimentary tract.

Since the two tests, one for cornified squames and the other for tryptic activity, depend upon fundamentally different processes the results of the two are likely to be more useful than that of only one.

Summary

It is again pointed out that children with congenital intestinal atresia can pass meconium which to the naked eye appears normal.

An attempt is made to assess the range of tryptic activity in normal meconium and to verify the basis of Farber's test.

It was found that in 92% of 142 specimens from 100 normal infants, tryptic activity was present in meconium to a dilution of at least 1 in 8. In five cases of intestinal atresia, tryptic activity was absent in four and present at a dilution of 1 in 2 in one case.

Meconium smears from 92 normal and four children with congenital atresia were stained as recommended by Farber and sent to three general clinical pathologists. Their reports were consistent and correct in only 16 of the 96 cases. This was found to be largely due to staining difficulties, and a more contrasting stain showed cornified squames in all smears but varying greatly in quantity. Squames were also found in small numbers in the smears from cases of atresia. Farber's test modified in this way should only be considered positive if large numbers of cornified squames are found.

If tryptic activity is absent in meconium, atresia below the ampulla of Vater or meconium ileus is likely. Tryptic activity present at a dilution of 1 in 8 or more would appear to exclude atresia below the duodenum.

It is recommended that in cases when the diagnosis of atresia is in doubt the meconium be examined both for cornified cells and for tryptic activity. Since the two tests depend upon fundamentally different processes the results of the two are unlikely to be equivocal.

A technical appendix is included.

Thanks are most sincerely accorded to the nursing staff of Nether Edge Maternity Unit for collecting specimens of meconium, and to the pathologists who examined the meconium films, Drs. Edwards, Gatman, Harding and Whitely, also to Mr. Robert Zachary for his interest and help, and to Nigel Blumsum for his voluntary technical assistance. The photographs were taken by A. K. Tunstall.

APPENDIX

Farber's Test

The following procedure was evolved for clinical use.

Make a thin smear of meconium from the inside of the specimen on a slide. If no meconium is available a rectal swab may be used. Put the smear immediately, or when dry, in a flat dish containing ether to dissolve the fat. Dry in air. Stain for one minute with 1% gentian violet or 1% methyl violet. Wash in running water. Decolorize in acid alcohol (5% HCl in 64·0 P. alcohol). Finally wash in water, blot, dry and mount. (Cornified squames are stained blue to violet; the background is colourless.)

Modified Stain for Cornified Squames

The technique is as follows.

Make smear, remove fat and dry as in the above method. Stain for two minutes in Masson's Ponceau-acid

fuchsin. Decolorize for 15 minutes in 1% phosphomolybdic acid. Counterstain for 15 seconds in 2% light green. Wash, dry and mount. Cornified cells stain red, and the background green.

Estimation of Tryptic Activity

Materials. The following are required: 5% sodium bicarbonate; 0·7 gelatine (prepared as in the Andersen-Early technique) made in bulk, and stored in medical flats; 37° C. waterbaths; small test tubes; wide-mouthed Wright pipette (marked at about 1 ml.); rubber teat.

Method. Put the gelatine to melt under a hot water tap. Using the Wright pipette, put 5% bicarbonate to the mark into a series of nine tubes in a rack. This same pipette, with a volume to the same mark, is used in all the subsequent dilutions and measurements. Add 5% bicarbonate to the meconium and mix to reach a consistency that can just be drawn up to the marked volume in the pipette. Transfer this to the first of the tubes containing bicarbonate, and mix by drawing up and down into the pipette. Transfer aliquot portions to the next tube, mix, and carry serial dilutions to the eighth tube discarding the aliquot portion at the eighth tube. The ninth tube is a control. Using the same pipette after washing in hot water, transfer volumes of the melted gelatine to each tube. Mix, incubate in a water bath for one hour, then place in running cold water and read when the control tube is seen to be completely solidified. (The tubes are also placed in the refrigerator overnight and reread in the morning.) Liquefaction is seen by tilting the tubes.

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FIBROCYSTIC DISEASE OF THE PANCREAS WITH MECONIUM PERITONITIS AT BIRTH

BY

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The relationship between meconium ileus and congenital fibrocystic disease of the pancreas is well recognized. Fibrocystic disease presenting with meconium peritonitis at birth is much less common and it is, therefore, considered justifiable to record a single case, especially as on this occasion the histological examination has been supplemented by serial sections of the main pancreatic ducts.

Case Report

L.M., a male infant, was delivered spontaneously on August 21, 1949, at full term, after a normal pregnancy, and weighed 6 lb. 10 oz. Both parents and one sibling were normal and healthy. At birth the infant's abdomen was large and tense (girth 37 cm. at six hours) and a right hydrocoele was present. He showed a mild degree of asphyxia, but respirations were established satisfactorily within a few minutes of birth. Shortly after delivery the child passed a single stool which was said to be 'mud-coloured', and he regurgitated mucus once. Because of the abdominal distension he was transferred to The London Hospital 30 hours after delivery. On admission his general condition was very good; temperature 98°F. pulse 140, weight 6 lb. 7 oz. There had been no further vomiting or passage of meconium. The abdomen was considerably enlarged and there were dilated veins over the upper abdomen and lower chest wall. There was an obvious fluid thrill in the abdomen, but no guarding or rigidity. Deep palpation was not possible because of the degree of distension, and on auscultation bowel sounds could not be heard. The umbilical stump was clean. The other systems were normal.

A blood count gave Hb. 133% (19·7 g. %); leucocytes 20,000 per c.mm (neutrophil-polymorphs 72%, lymphocytes 25%, eosinophils 2%, monocytes 1%).

A radiograph of the abdomen showed a large air-containing loculus with a fluid level in the right upper quadrant, extending as high as the dome of the diaphragm (Fig. 1). A diagnosis of intestinal obstruction was made, and it was thought that peritonitis was probably also present.

The child was given a slow intravenous drip of $\frac{1}{5}$ normal saline in 4% glucose solution, and a laparotomy under general anaesthesia was performed by Mr. J. E. Richardson. Large quantities of turbid brown fluid escaped as soon as the peritoneal cavity was opened. The loops of the small intestine were matted together and were closely adherent to the left side of the abdomen. There was no evidence of distension of the bowel and no perforation was seen, although adequate exploration of the abdomen was impossible.

The child died within a few hours of the operation.

Microscopy of the peritoneal fluid showed the presence of numerous pus cells, and on culture a pure growth of *Bact. coli* was obtained.

Necropsy Report

The findings of the necropsy (P.M.311/49) may be summarized as general peritonitis, perforation of the transverse colon and cystic fibrosis of the pancreas.

Peritoneal Cavity. No free fluid was present but coils of small intestine and part of the large intestine

FIG. 1.—Radiograph of abdomen showing air and fluid level beneath right dome of diaphragm.

were united by stiff, greenish-brown exudate (up to 0·2 cm. thick) suggesting fibrin containing some meconium. A similar exudate was present on the anterior and inferior surfaces of the right lobe of the liver, in patches on the parietal peritoneum of the right side and in the left iliac fossa, but was scanty in the left hypochondrium.

Alimentary Tract. There was a perforation (0·2 cm. diameter) in the wall of the transverse colon near the splenic flexure, the margin on the serosa being slightly raised and surrounded by a zone (0·1 cm. wide) of prolapsed mucosa; on the mucosal side the hole was filled by a plug of inspissated meconium. Similar meconium in small pieces was seen in the jejunum, and in larger pieces in the caecum and appendix, but was very scanty elsewhere and absent from the rectum; all of it was yellowish-brown, firm and stiff, the usual slimy consistency being noticeably absent. There was slight distension (up to 2·5 cm. diameter) of the rather turgid lower ileum but not of the remaining intestine. There was no evidence of obstruction within or outside the lumen of any part of the intestine.

There was slight congestion of the pancreas. No obstruction to the common bile duct was seen. There were orange uratic streaks in the medulla of the kidneys. There was central congestion of the suprarenals, with haemorrhage in the capsule of the right. A few petechiae were seen on the surface of the thymus and thyroid. There were scattered patches of collapse in congested lungs, but no abnormality in the trachea and main bronchi. A few millelitres of greenish-yellow fluid were found in both pleural cavities and in the pericardial sac. There was a centre of ossification (0·5 cm. diameter) at the lower end of the femur. The body was that of a normal-sized, three-day-old male (5 lb. 13½ oz.).

Weights of Organs. Heart, 16 g.; liver, 112 g.; kidney, 27 g.; suprarenals, 9 g.; spleen, 6·8 g.; brain, 427 g.; thyroid, 1·4 g.; thymus, 4·4 g.; testis, 0·5 g.

Microscopical Examination. Portions of the pancreas (head, body and tail), lung, right middle and lower lobes, left lower lobe, trachea, stomach with cardia, lower oesophagus, appendix, colon at site of perforation, testis, thyroid, right and left suprarenals, prostate, thymus, kidney, liver, right lobe, spleen and rib were fixed in formol-saline, embedded in paraffin, and stained with haematoxylin and eosin and with iron haematoxylin and van Gieson. A selection of tissues was also stained by the periodic-acid-Schiff (P.A.S.) method using watery solutions. In addition serial sections were made of the head of the pancreas and adjacent duodenum to include the terminal parts of the main pancreatic and common bile duct.

The most important finding was the fibrocystic change in the pancreas. The glands of the trachea and main bronchi contained abundant mucin; changes in other organs were slight.

PANCREAS. All sections showed a severe degree of fibrocystic disease, the changes being of uneven degree in different parts of the organ and in different parts of any one section but on the whole most advanced in the head. There was considerable dilatation of interlobular and interacinar ducts, their epithelium being flattened and their lumina empty or containing bright eosinophil secretion (Fig. 2); in a few there were collections of partly necrotic polymorphonuclear leucocytes. In places the individual cells of the acini were atrophied; only a few acini contained retained secretion. There was widespread oedema, and patchy fibrosis between acini was more marked between lobules (Fig. 3) and associated with foci of dilated capillaries and lymphocytic infiltration. Acute inflammation was not seen in the interstitial tissue. The islets of Langerhans were not conspicuous but they showed no change.

In serial sections of the head and attached duodenum the mucosa of the common opening of the duct of Wirsung and the bile duct was deeply folded; at 375-750μ from the tip of the ampulla the lumen of the bile duct was star-shaped, that of the duct of Wirsung appearing as numerous spaces between columns of fibrous tissue (Fig. 4). Further back the ducts were round or oval with small diverticula branching from the main lumina, these being more prominent in relation to the bile duct. The main pancreatic duct was not dilated, and at 2·6 mm. from the tip of the ampulla it could not be distinguished with certainty from some of its branches. There was no evidence that the duct of Wirsung was stenosed; the appearance in Fig. 4 is probably due to partial tangential section of a plicated epithelium. (A plicated epithelium was seen in the terminal portion of the main pancreatic duct in material obtained from a control full term foetus, and in places the duct also appeared as multiple spaces in section.)

ALIMENTARY TRACT, SPLEEN AND LIVER. In the section through the perforation in the transverse colon the mucosa was prolapsed through to the serosa (Fig. 5) with very little reaction about it. The adjacent muscularis was oedematous as in the section of the appendix. One gland in the mucosa of the appendix was considerably dilated with retained secretion. The peritoneum over the appendix, that over the capsule of the liver and one area over the spleen showed an organizing exudate in which histiocytes, lymphocytes, dilated capillaries, a little delicate collagen and a very few small foreign

body giant cells were present (Fig. 6). Also in the exudate, and presumably derived from meconium, were some pigmented bodies, a few epithelial squames and a very few refractile bodies of uncertain nature, some of which were related to the foreign body giant cells. There was slight fatty change in the parenchyma of the liver and congestion of the splenic pulp.

RESPIRATORY SYSTEM. The section of the left lower lobe showed areas of collapse. Both here and in the right middle and lower lobes many bronchi and alveolar spaces contained hyaline, eosinophil, amorphous necrotic material including refractile squames and occasional foam cells containing sudanophil droplets. There was abundant mucin in the cells and lumina of glands related to the main bronchus to the left lower lobe; one of these was dilated (Fig. 7). A transverse section of the trachea showed similar abundant mucin and also focal necrosis of its mucosa with replacement of the latter by inflammatory tissue.

Other organs showed no significant changes.

Discussion

The cause of death in this case was clearly the peritonitis, and this was obviously due to the leakage of meconium through the perforation in the transverse colon. The appearances of the exudate indicated that it was at least three or four days old, which would be compatible with a perforation occurring shortly before or during delivery.

Peritonitis occurring in the child before birth or in the first few days of life is a very uncommon event. Simpson (1838), however, reported details of 25 cases, and in recent years Abt (1931) and Thelander (1939) have published extensive reviews of the subject. The majority of case reports do not indicate clearly the aetiology of the condition, although in most there has been evidence of an escape of meconium into the peritoneal cavity.

Meconium peritonitis can result from leakage through a congenital defect in the intestinal wall, such as a patent Meckel's diverticulum, but is more often a sequel to intestinal obstruction. The latter may be due to mechanical factors such as congenital

FIG. 2.—Retained secretion within a dilated duct of the pancreas, round cell infiltration in surrounding connective tissue. H. & E. × 130.

FIG. 3.—Fibrosis between and within lobules of the pancreas. Van Gieson × 82.

FIG. 4.—Terminal part of duct of Wirsung (numerous small spaces) and of common bile duct (star-shaped) in partial tangential section about 500μ from tip of the ampulla of Vater. Van Gieson × 17.

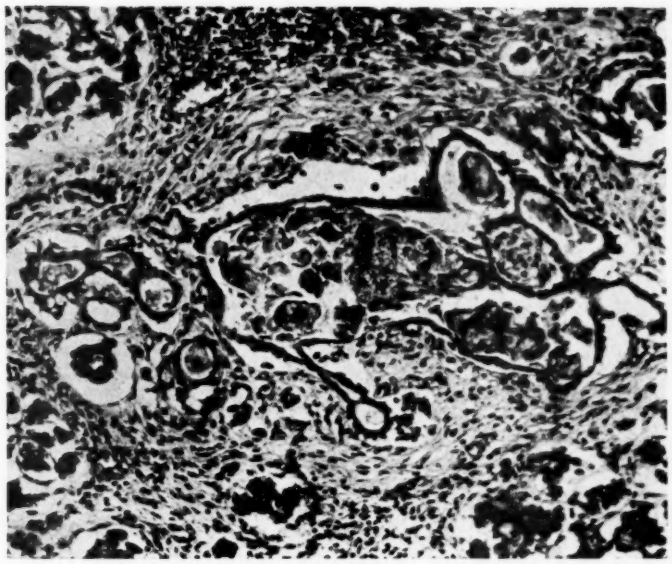

FIG. 2.

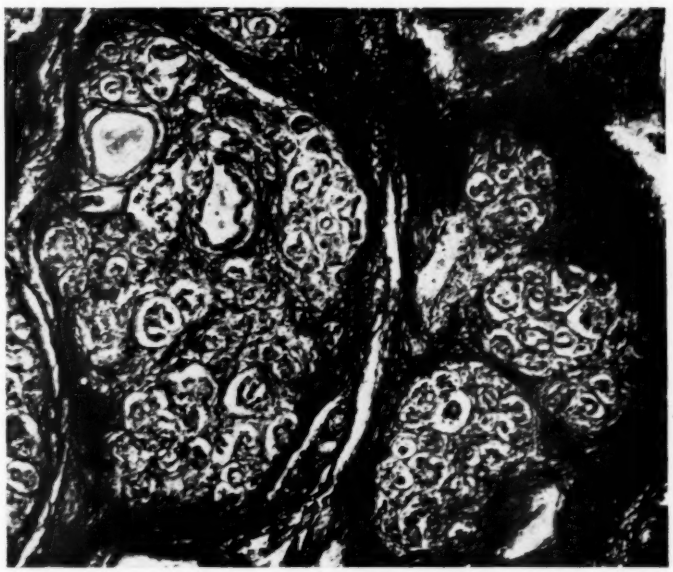

FIG. 3.

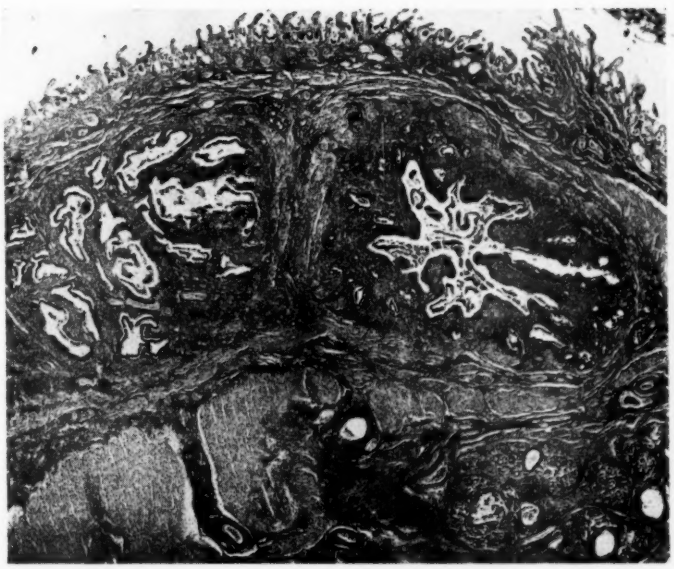

FIG. 4.

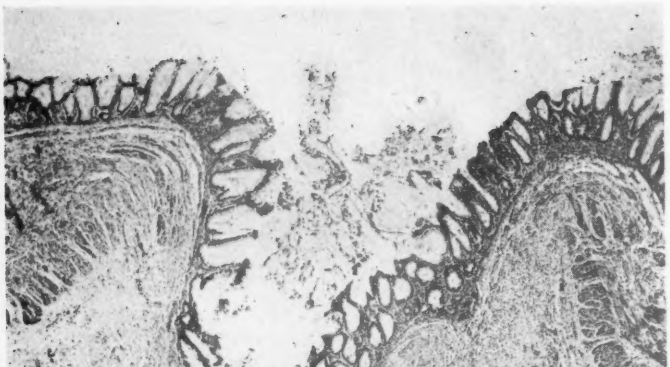

FIG. 5.

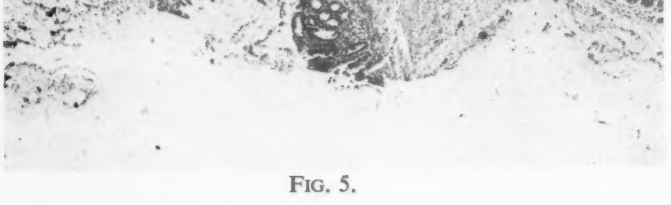

FIG. 6.

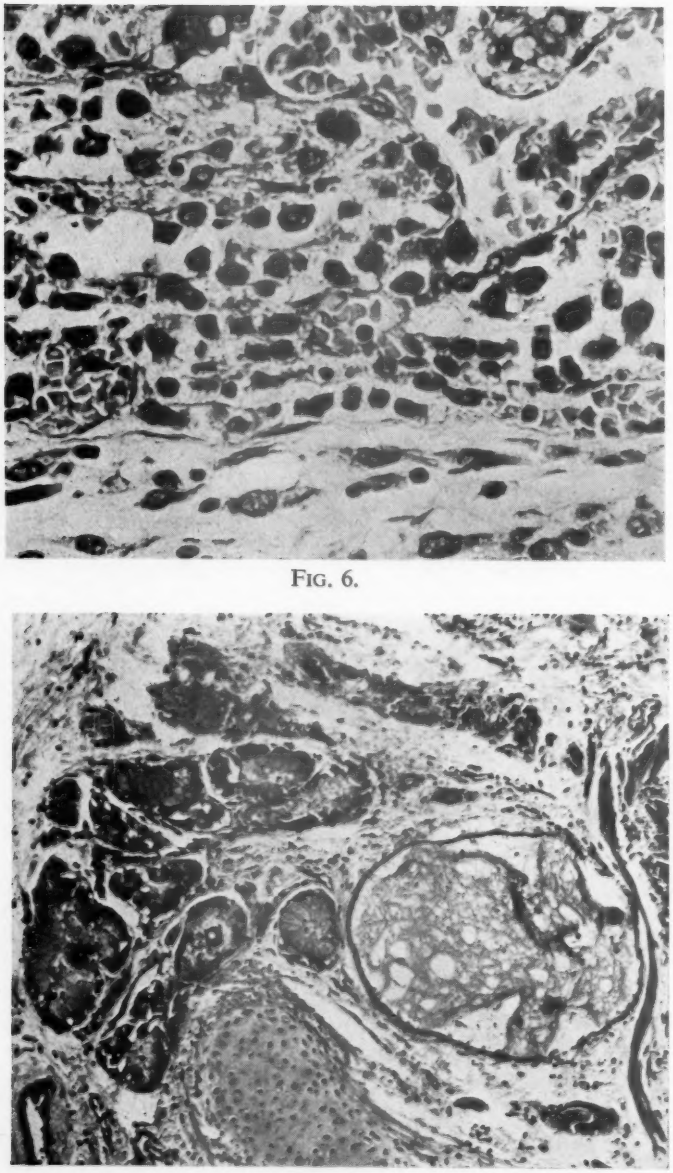

FIG. 7.

stenosis or obstruction by bands, to a combination of mechanical factors and impaction and inspissation of normal meconium (Farber, 1944a), or to impaction and inspissation of abnormal meconium alone. In the present example the residual meconium in the intestine appeared abnormal to the naked eye and the change in the pancreas is important circumstantial evidence in favour of this. At necropsy definite evidence of intestinal obstruction was not found; but the perforation in the colon was of the ' blow through ' type, such as can occur at a weak point in the intestinal wall above an obstruction. Such a weak point would be the place of penetration through the muscularis of entering vessels. The splenic flexure is an obvious place where abnormal meconium might become impacted, but this is an uncommon finding in cases of meconium ileus, in which the site of obstruction is usually at the lower end of the ileum.

We have been able to trace reports of 12 cases of intestinal obstruction associated with cystic fibrosis of the pancreas in the newborn, and of these, that of Kornblith and Otani (1929) is the only one in which impaction of meconium was thought to have occurred in the large intestine. In this case there was also evidence of obstruction at the terminal ileum, which was the site of obstruction in ten of the others; the twelfth, one of those reported by Andersen (1938), was an example of atresia of the jejunum. In the case of Kornblith and Otani there were two perforations of the 'blow through' type in the ascending colon and also a false diverticulum. These authors postulated an obstruction at the hepatic flexure but, as in the present instance, there was no definite evidence of this at necropsy. They discussed the mechanism of perforation in some detail, suggesting that false diverticula first form and then perforate. Active peristalsis is known to occur in the foetus after the fifth month of intrauterine life (Windle, 1940), hence prenatal obstruction and perforation of the intestine is possible. Abnormal meconium probably plays some part in the perforation but it is unlikely that it could penetrate the wall of the colon in the absence of obstruction.

Landsteiner (1905) was the first to report the association of meconium peritonitis with fibrocystic

FIG. 5.—Perforation in transverse colon. H. & E. × 17.

FIG. 6.—Exudate on surface of liver. Numerous mononuclear cells between dilated capillaries. H. & E. × 480.

FIG. 7.—Main bronchus to lower lobe of left lung. Retained mucus in dilated duct of mucus gland. H. & E. × 97.

disease of the pancreas. It is now generally accepted that the abnormal meconium is due to an absence of pancreatic secretion from the intestine, although recent evidence suggests that an abnormal protein in the meconium may be responsible for its peculiar consistency and the difficulty of its passage along the intestine (Glanzmann and Berger, 1950). There are two main theories concerning the mechanism of the retention of secretion within the pancreas. The well documented examples of Kornblith and Otani (1929) and of Hurwitt and Arnheim (1942) are usually accepted as cases of meconium ileus in which fibrocystic disease of the pancreas was due to a stenosis of the terminal part of the duct of Wirsung of developmental origin. In the present material, serial sections of this area showed a curious and striking splitting of the lumen of the duct into clefts separated by fibrous tissue septa (Fig. 4) but there still appeared to be ample space for the free passage of secretion. Reference to the paper of Kirk (1944) on the normal anatomy of the common opening of the pancreatic and bile ducts into the duodenum suggested that this appearance was normal. Examination by serial sections of a similar area in a control full term foetus showed an essentially similar appearance, although the number of separate lumina in the control was smaller, possibly because in the latter the sections were at right angles to the axis of the duct, whereas in the material from the case under investigation the sections were partly tangential. Kirk (1944), in his description of the mucosa in the common opening of the ducts into the duodenum, compares the arrangement to the plication of the oviduct and suggests that it may have some function in preventing duodenal fluid regurgitating into the ducts. We would agree with this and do not consider that this plication causes obstruction. The appearances resemble in some ways those described by Kornblith and Otani (1929), and Hurwitt and Arnheim (1942), but the striking dilatation of the duct in the body of the pancreas described by them was not seen. There is no evidence from the present material of a mechanical obstruction in the main pancreatic duct. Baggenstoss, Power and Grindlay (1951) have claimed that there is atresia of numerous interlobular ducts and that this accounts for the changes in the pancreas. In our material some of the smaller ducts appeared to end blindly in fibrous tissue, but there was no indication of any persistent solid columns of epithelial cells such as might be expected in atresia. We think it more likely that secondary obliteration of ducts occurs. The explanation of Farber (1944b) that the obstruction and consequent dilatation of smaller ducts is due to an abnormal inspissated secretion appears to us to be more likely. This author mentions the frequent occurrence of abnormal secretions in other glandular tissues. We can find no definite evidence of this in our case. Secretion within mucous glands of the trachea and the main bronchus to the left lower lobe is abundant, but not more excessive than has been seen in some controls of the same age dying with respiratory infection or after inhalation of foreign material. In this infant, asphyxia was present at birth and the sections of lung showed hyaline necrotic material in many small bronchi, so that inhalation of amniotic fluid may have occurred. Furthermore, a general anaesthetic with endotracheal intubation had been given. No other indication of retention of secretion was seen in the many tissues examined, except for distension of one gland in the appendix, and this might have been caused by the intestinal obstruction. Unfortunately examination of salivary glands was omitted.

The clinical features of our case were of some interest. On admission, examination of the child's abdomen showed no true guarding or rigidity. Moreover, his general condition remained good until the time when the abdomen was opened and was found to be full of purulent fluid. These features are in keeping with one's experience of peritonitis in small infants, that is to say the clinical signs of peritonitis may be lacking and the general picture unrelated to the degree of peritoneal inflammation found at operation or necropsy. They may, perhaps, be explained by the fact that, although meconium peritonitis was probably present at birth, bacterial infection would not have taken place until after delivery. In addition, the fluid requirements of such a young infant would be small, and in this particular child fluid loss, apart from the formation of peritoneal exudate, was negligible. The absence of vomiting was noteworthy, and suggests that perforation of the colon and relief of intestinal obstruction had occurred at or before delivery; the appearance of the peritoneal exudate at necropsy lends support to this view.

Summary

A case of meconium peritonitis in association with fibrocystic disease of the pancreas in a newborn infant is reported.

Careful examination of the main pancreatic duct by serial section revealed no mechanical obstruction or stenosis.

Features of particular interest were the presence of abdominal distension at birth; the absence of vomiting, which is usually a prominent feature of most cases of meconium ileus; and the unusual site of intestinal perforation.

Reasons are given for our view that this perforation occurred before or during labour.

We are indebted to Dr. R. H. Dobbs for permission to publish this case and for helpful criticism, to Professor D. S. Russell for advice, and to Professor J. D. Boyd for information concerning the normal development and anatomy of the pancreatic ducts. We are also grateful to the technicians of the Department of Anatomy who prepared the serial sections.

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CHYLOUS ASCITES IN INFANCY

BY

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Chylous effusions into serous cavities are interesting occurrences especially as they affect infants. A milky effusion into the peritoneal cavity is extremely rare in early life. Wallis and Schölberg (1911) collected 173 cases of milky ascites in all age groups. Of these only three occurred in infants under 1 year of age. Witt (1924) mentions 187 cases recorded between 1691 and 1916 of which only 29 occurred in children. In 1922 two further cases were recorded by Scherer and by Schall, both in infants under 1 year. Of this total of 31 cases in children, nine were under 1 year of age, eight occurred between the ages of 1 and 5 years, and the remaining 14 were in the age group 5 to 12. The youngest, a neonate of 16 days, was reported by Kerr (1909). The original collection of 53 cases of chylous ascites, occurring in all age groups, and covering the period 1699-1889, was recorded by Busey (1889). Cowie (1911) collected eight cases of this affection in infants and added one of his own. Five of these were under the age of 12 months and the remaining four were in the age group 12 to 32 months. Cowie's series includes the first case ever reported, that of Morton (1691). This case was recorded in Latin and translated for Cowie by Professor Meader: the patient was a boy of 2 years, and the description mentions 'a distended abdomen which increased daily'. The child developed 'a severe marasmus' but 'retained a robust and handsome appearance'. 'His appetite was substantial, if anything inclined to voraciousness, up to the very day of his death.' From these acute observations Morton correctly concluded that the ascites was chylous and that the inanition resulted from 'the withdrawal of the nutritious fluid due to the body, from the chyliferous ducts'. The abdomen was tapped and 'several pounds of lactescent chyle, just as sweet as is found in the chyle duct itself' were removed. The necropsy findings in this case suggested tuberculosis as the causative factor.

Nieuwondt and Rozenzweig (1892) described a case from Cape Town, South Africa, that of a girl of 15 months of age from whom 20,400 ml. of milky fluid were tapped from the peritoneal cavity on 11 occasions. The fluid had a specific gravity of 1012, was neutral, white and creamy, and had a sweetish odour. The authors considered that the fluid only slightly resembled the general character of chyle, and that the condition was due to attacks of peritonitis. Kerr's (1909) case was a boy aged 16 days. In this child 1,140 ml. of a milky-white, odourless fluid were removed. The cause was given as congenital syphilis, and the abdominal distension was associated with chyluria.

Case Report

A Bantu girl aged 11 weeks was admitted to hospital under my care on November 8, 1950. The diagnosis of the admitting officer was 'abdominal distension'. The history given by the mother was that the child had been born in a maternity hospital and had been 'swollen' from birth. The mother herself had had toxaemia of pregnancy and remained in the hospital for 23 days after confinement. She stated that the swelling of the child had subsided by the time she left the maternity centre, except for the abdomen, which became progressively larger. The infant was breast-fed and there was no abnormality in the bowel actions or micturition. There was one other child in the family; he was healthy, as was the father.

The infant appeared to be a fairly well-nourished, contented child. On admission the weight was 11 lb., and the temperature 98·4°F. (rectal).

The head was normal in size and shape. The throat appeared normal, as did the ear-drums. There were no palpable glands in any area. Nothing abnormal was detected in the cardiovascular, respiratory or nervous systems. Examination of the abdomen revealed marked distension. Dilated veins were seen on the anterior abdominal wall. Shifting dullness was present and a fluid thrill was easily felt. The external genitalia appeared to be swollen and there was a left inguinal hernia. On

account of the marked distension of the abdomen no organs could be felt. Rectal examination did not reveal any abnormality.

There was obviously a large amount of fluid in the peritoneal cavity and paracentesis was performed on the day after admission, 26 oz. of a white fluid similar to milk being removed. It was clear that this was probably a case of chylous ascites.

Analysis of the fluid showed:

Total solids	14·2 g. %
Ash	0·67 g. %
Protein	4·1 g. %
Lactose	absent
Fat	4·1 g. %
Calcium	0·011 g. %
Chloride	0·36 g. %

The cholesterol content of the fluid was 170 mg. per 100 ml. This analysis is typical of chylous fluid. Microscopical examination of smears from the fluid showed a moderate number of lymphocytes and an occasional serosal cell. No malignant neoplastic cells were observed.

Examination of the urine on admission showed no albumin, acetone or sugar. Microscopy showed a large number of epithelial cells with about seven pus cells per high power field (non-catheter specimen).

A blood count gave the following result: haemoglobin, 11·9 g. %; erythrocytes, 3,560,000 per c.mm.; leucocytes, 8,000 per c.mm. The blood cholesterol level was 185 mg. per 100 ml., which was 15 mg. higher than that of the chylous fluid.

A serum protein estimation gave total proteins, 4·9 g. %; albumin, 2·7 g. %; globulin, 2·2 g. %.

Radiological examination of the chest showed nothing abnormal.

The weight of the child dropped to 9 lb. 8 oz. after the paracentesis. With the removal of the fluid, the abdomen was easily examined but the liver and spleen were not felt.

Distension of the abdomen reappeared so rapidly that by the fourth day after the paracentesis it was as distended as on admission. Paracentesis was again performed and 20 oz. of the same type of fluid were removed. After this removal the fluid seemed to accumulate more slowly. Eighteen days after the second removal of fluid, the procedure was repeated, and on this occasion 24 oz. of similarly milky fluid were removed. The serum protein level at this stage had increased to 5·3 g. per 100 ml. from the previous level of 4·9 g. A further examination of the urine for chyluria was negative. The urine, which was slightly turbid, was water-clear after centrifuging, which suggested that the turbidity was not due to emulsified fat.

After the third paracentesis the child was discharged on the mother's insistence, but was returned to hospital three weeks later with the abdominal distension as gross as before. It had obviously recurred more slowly. A fourth paracentesis was performed, and on this occasion 34 oz. of milky fluid were removed. The weight of the infant after the removal of the fluid was 10 lb. 14 oz., compared with 9½ lb. after the first paracentesis 45 days before.

The child was discharged from hospital with instructions to report back at intervals. Eighteen days after the last paracentesis she was brought back with obvious whooping cough complicated by bronchopneumonia. She died on the day of admission.

Necropsy. This was performed by Dr. J. Higginson. The body was that of a Bantu female infant. The right pleural sac had some fibrous adhesions, the left being normal. Both lungs showed moderate congestion with numerous petechial haemorrhages scattered over the pleural surfaces. There was no evidence of dilated lymphatic ducts in the thorax. The pericardium and heart were normal.

The peritoneal sac contained 1 pint of white, milky fluid. The spleen was congested and the kidneys appeared normal, as did the rest of the genito-urinary tract. The liver weighed 150 g. and showed no obvious lesions except for irregular congestion. The gall bladder was healthy. The stomach was normal except for numerous white dilated lacteals along its lesser curvature. The intestinal tract appeared healthy, but several dilated lacteals were noted in the upper portion of the jejunum. There was no dilatation of the cisterna chyli. Histological examination of the lymph channels and nodes around the aorta showed that the channels were widely dilated and filled with lipoid-containing macrophages. A fat stain on the lesser curvature of the stomach showed a very large number of small sudanophil droplets lying in the external portion of the muscle wall and in the subserosal layer. The histological features suggested that there was obstruction of the lymphatic drainage at the level of the diaphragm.

Discussion

This case was clearly one of chylous ascites in an extremely young infant. The diagnosis could only be made by removing fluid from the peritoneal sac. A total of 104 oz. of the milky-white chyle was removed by four tappings, and in addition another 20 oz. were found in the peritoneal sac at necropsy. Notwithstanding the great loss of chyle, the child gained 1 lb. 6 oz. in about six weeks.

Various causes have been given to account for the accumulation of chylous fluid in the peritoneal cavity. Busey (1885) cites Morgagni's reference to the cases of Valsalva and Santorino, in which the thoracic duct was blocked by an aneurysm. Busey (1885) also cites Virchow's reference to his case in a newborn calf after a thrombosis of the external jugular vein, occluding the mouth of the thoracic duct. Traumatic rupture of the thoracic duct is a potent cause of the condition. Pure chyle, as it flows from the thoracic duct, is a milky, opaque fluid, slightly alkaline, with a specific gravity between 1007 and 1043, usually not higher than 1025. About 4% of the thoracic duct chyle is made up of protein. The fat content varies with the food intake and the protein is made up of serum albumin and globulin. About 10% of chyle is made up of fat,

protein and salts, and the rest water. An interesting fact is that in the analysis of the fluid in the case recorded here, the total solids, protein and fat values lay within the same range as human milk (on which this patient was being fed), but the ash, calcium and chloride values were outside recognized limits of breast milk; in addition, lactose, a normal constituent of milk, was absent from the chylous fluid. Rous (1908) mentioned that cases of chylous effusions should exhibit a reduced total lymphocyte count in the blood, as the thoracic duct is the chief pathway of lymphocytes to the blood stream, although small numbers enter directly in the marrow.

Chylous ascites is a condition which must be differentiated from a chyliform effusion which occurs in such conditions as tuberculous peritonitis or peritoneal carcinoma. The analysis of the fluid in the present case conformed to that of a true chylous effusion, and the necropsy findings suggested the presence of a congenital anomaly of the lymphatic drainage of the intestinal tract. Chylous ascites is a very rare condition at any age, but particularly in early infancy. It should be regarded as a symptom-complex with various aetiological factors at play in different cases. In the case described, it appeared that tappings were required at longer intervals, and that the fluid was accumulating more slowly after each successive paracentesis. The weight of the child improved and also the serum protein level. If the child had not died from whooping cough, it is possible that the condition might have improved with repeated tappings at more infrequent intervals.

Summary

A case of chylous ascites is described occurring in a Bantu girl in the third month of life. Altogether 104 oz. (3,120 ml.) of this fluid were removed by four successive abdominal tappings, and in addition a further 20 oz. (600 ml.) were found in the peritoneal cavity at necropsy. On analysis the fluid was shown to resemble true chyle. Histopathology suggested a congenital anomaly of the lymphatic drainage of the intestinal tract as the aetiological factor.

I wish to thank Dr. J. D. Allen, Medical Superintendent, for permission to report this case. Thanks are also due to Dr. J. Higginson for the necropsy and histological examinations, Dr. C. Glynn Williams for his help in attending to this case, Dr. H. Hirsch for laboratory investigations, Mr. S. Kay for helpful advice, Dr. A. R. P. Walker for his analysis of the fluid, and finally to Drs. H. Stein and S. Burgin for their careful case-notes.

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VASCULAR ABNORMALITIES ASSOCIATED WITH PSEUDOXANTHOMA ELASTICUM

BY

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Evidence has been presented by several authors that the skin condition known as pseudoxanthoma elasticum may be associated with widespread abnormalities of the blood vessels of the limbs and viscera (Sandbacka-Holmström, 1939; Touraine, 1940, 1941; Carlborg, 1944; Guenther, 1946; Scheie and Freeman, 1946; Revell and Carey, 1948).

The term pseudoxanthoma elasticum was first used by Darier (1896) to describe a dermatological condition characterized histologically by degeneration and fragmentation of the elastic tissue in the dermis. Clinically, the skin becomes flaccid and can be lifted off the underlying tissue to an abnormal degree. When it is stretched, yellow or flesh-coloured papules and irregular streaks become visible in the affected region. The yellow discoloration has given rise to the term pseudoxanthoma but apart from this superficial resemblance the condition is not related to xanthomatosis. The lesions are more or less symmetrically distributed and are commonly found in the neck, axillae and groins but may occur elsewhere, particularly on the abdomen and in the antecubital and popliteal fossae. The condition usually starts before the age of 30 and may be familial (Cockayne, 1933).

The first indication that the changes in the skin are part of a more generalized abnormality was the discovery by Grönblad (1929, 1932) and Strandberg (1929) that pseudoxanthoma elasticum is frequently associated with angioid streaks in the fundi. This association has since been known as the Grönblad-Strandberg syndrome. Angioid streaks are brown, reddish or grey streaks which are found near the disc or radiate from it towards the periphery. Retinal haemorrhages, particularly at the maculae, and evidence of retino-choroidal degeneration may also be present and may at times be found even in the absence of angioid streaks (Batten, 1931; Benedict and Montgomery, 1935).

The nature of angioid streaks has been discussed by several authors including Batten (1931), Benedict and Montgomery (1935), Franceschetti and Roulet (1936), Law (1938), Scholz (1941), Ebert (1943), Winkelman (1948) and Verhoeff (1948). Duke-Elder (1940) considers that angioid streaks are probably the result of ruptures in the elastic membrane of Bruch of the choroid. This view is supported by the histological findings of Böck (1938) and Hagedoorn (1939), and more recently by Verhoeff (1948), all of whom found degenerative changes in the elastic tissue of Bruch's membrane and breaks in its continuity.

In addition to the degeneration of elastic tissue in the skin and choroid, similar changes have also been demonstrated in the aorta and brachial arteries (Urbach and Wolfram, 1938) and in the vessels of the jejunum and ileum and, to a lesser extent, in the coronary arteries (Prick, 1938). These findings were based on post-mortem studies of two patients with pseudoxanthoma elasticum and angioid streaks who died at the ages of 44 and 48. The changes in the elastic tissue of the blood vessels were similar to those seen in the skin and choroid and were not thought to be due to arteriosclerosis. Touraine (1940, 1941) puts forward the view that the skin changes of pseudoxanthoma elasticum are only one aspect of a widespread familial disorder of elastic tissue affecting the skin, the eyes and the blood vessels. He refers to this disorder as 'l'élastorrhexie systématisée'. Böck (1938) and Parkes Weber (1948) use the term 'elastosis dystrophica' to describe the same condition.

There is a considerable amount of clinical evidence to support the view that the peripheral blood vessels are involved in the pathological process underlying pseudoxanthoma elasticum. In a monograph on the circulatory abnormalities in the arteries to the limbs Carlborg (1944) has reviewed the literature, and he was able to demonstrate diminished pulsation and a reduced pulse wave

velocity in 14 out of 15 patients with pseudoxanthoma elasticum. Four of his 15 patients had definite symptoms of intermittent claudication which had begun at the age of 18 in one case, at 36 in another and during the fifth decade in the remaining two. Intermittent claudication since childhood has been reported in a man with pseudoxanthoma elasticum and angioid streaks (Scheie and Freeman, 1946). When this patient was examined at the age of 26 no pulsation could be felt in either the dorsalis pedis or posterior tibial artery. Calcification was visible radiologically in the arteries of the thighs. Several of Carlborg's cases also had calcification in the arteries of the limbs. In two of these the calcification was demonstrated at the ages of 27 and 32. All the others were over 40.

The clinical evidence of involvement of the visceral blood vessels is less complete. Carlborg (1944) draws attention to the fact that several of his patients had symptoms suggestive of angina pectoris. As most of these patients were over 40, arteriosclerotic changes could have been responsible for these symptoms as well as for the calcification in the peripheral arteries mentioned previously.

Gastro-intestinal haemorrhages have been reported in association with pseudoxanthoma elasticum by several authors. Thus in one patient haematemeses occurred at the ages of 17 and 18 (Carlborg, 1944, case 2), and in another five times between the ages of 24 and 35 (Chauffard, 1889). Terminal bleeding into the gastro-intestinal tract was seen by Tannenhain (1901) in an arteriosclerotic woman aged 74, and by Hagedoorn (1939) in a woman aged 48. Revell and Carey (1948) report a patient with pseudoxanthoma elasticum and angioid streaks who had a haematemesis at the age of 14, two further ones at the age of 29 and melaena at the age of 30. The same authors report another patient in whom a profuse gastro-intestinal haemorrhage occurred at the age of 28 and in whom pseudoxanthoma elasticum was associated with angioid streaks, hypertension and absent peripheral pulses. They suggest that the haemorrhages in these two cases were due to ' systemic pseudoxanthoma elasticum '.

A boy in whom pseudoxanthoma was associated with fundal changes, absent peripheral pulses, intermittent claudication and recurrent gastro-intestinal haemorrhages has been under observation by one of us (B.E.S.) since 1945 when he was 9 years old. This appears to be the first case in which all these abnormalities have been found in the same patient and at such an early age.

Case Report

G.R. was a 9-year-old boy when he was first seen at The Hospital for Sick Children, Great Ormond Street, in August, 1945. He complained of pain in the calves which came on whenever he was running or walking fast. Apart from the fact that the skin on the abdomen was unusually lax, no abnormality was noticed on examination. A radiograph of the hip joints was normal but revealed calcification in both femoral arteries.

FIG. 1.—Lax, inelastic skin on the abdominal wall due to pseudoxanthoma elasticum in a boy aged 9.

In June, 1947, he was admitted to the hospital on account of a sudden onset of melaena. He was pale and weak. The skin was abnormally lax on the abdomen (Fig. 1) and to a lesser extent also in the neck, axillae, antecubital fossae and in the upper parts of the thighs. Yellowish flecks were seen in the skin in the same areas. There were numerous small dots around the discs, at the maculae and in the periphery of the fundi (Fig. 2). Some of these dots were ill-defined and yellow, others were white and glistening. There was some pigmentary degeneration and small areas of choroido-retinal degeneration were present. No angioid streaks were seen. Both radial pulses were absent. The liver was palpable. Otherwise clinical examination revealed no abnormality.

Haemoglobin was 60% with 2,800,000 red cells per c.mm. The white cell and platelet count, bleeding and clotting time, and the bone marrow were all normal. A chest radiograph showed fine, uniform punctate opacities which were distributed evenly throughout the left lung fields (Fig. 3). The right lung was normal. A radiograph of the skull was normal. The blood cholesterol was 209 mg. per 100 ml. Biopsy of the skin (Fig. 4) showed the typical changes of pseudoxanthoma elasticum. The elastic fibres were fragmented and condensed into irregular whorls. An electron micrograph taken later demonstrated that despite this abnormal arrangement of fibres the component fibrils were normal in appearance (Fig. 5).

He was treated with a blood transfusion and iron, and discharged after three weeks with a haemoglobin of 95%. He had a further small haematemesis followed by melaena in February, 1948, and a larger one in April, 1948, when he had to be readmitted. Haemoglobin had

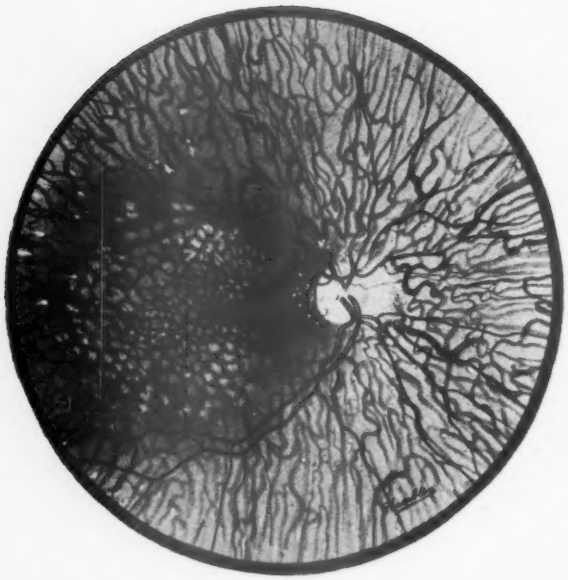

FIG. 2.—Drawing of the fundus of the same patient showing pale dots thought to be colloid bodies and areas of pigmentary degeneration.

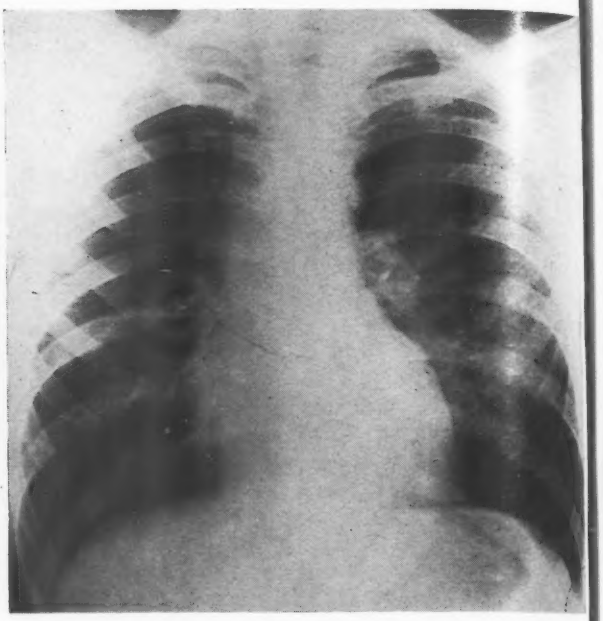

FIG. 3.—Chest radiograph showing miliary mottling in the left lung fields of the same patient.

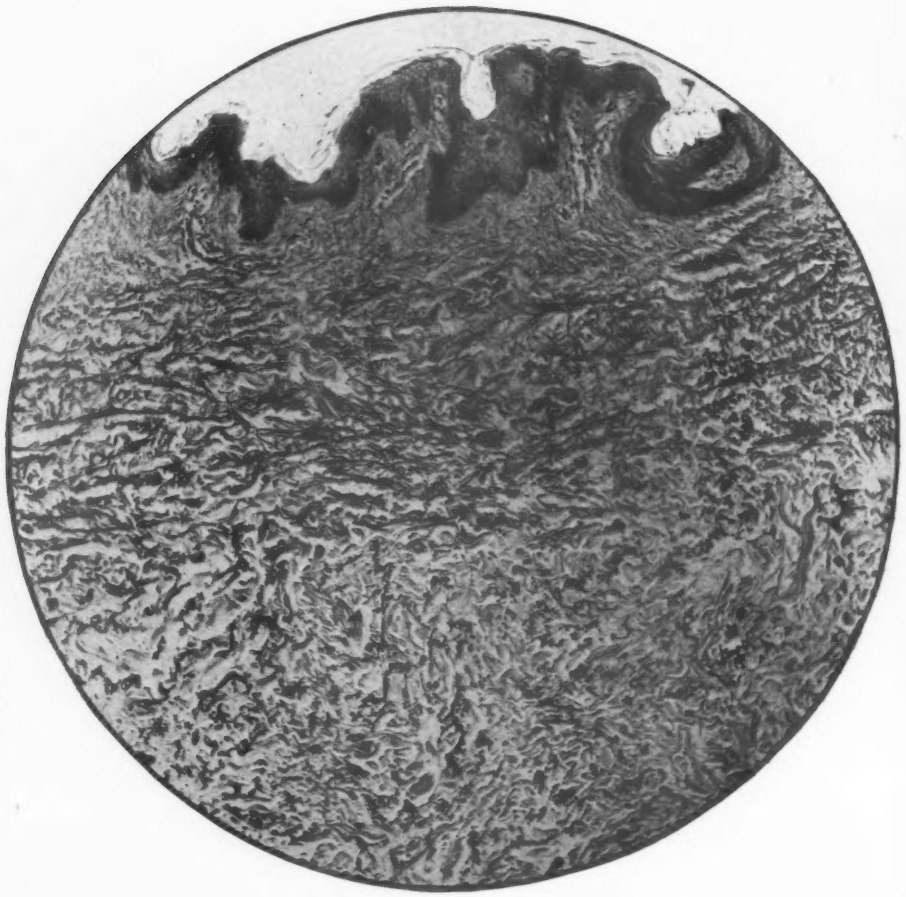

FIG. 4.—Biopsy of the skin showing fragmentation of the elastic tissue (Lawson's elastic stain × 45).

FIG. 5.—Teased out subcutaneous tissue showing that the component fibrils of the elastic fibres are normal in structure. (Electron photomicrograph ×45,000.)

fallen to 68% and he was again treated by transfusion. A barium meal and barium swallow in July, 1948, revealed no abnormality. A further small haematemesis occurred in March, 1949.

In April, 1950, he was admitted to University College Hospital. Three days before admission he had suddenly felt faint and sick. The next day he vomited blood and his motions became loose and black. He was still complaining of pain in the calves on rapid walking. The pain was always relieved by standing still. It never came on at rest or when he was walking slowly.

On admission he was pale but not shocked. The skin condition was essentially unchanged. The fundi revealed the same changes which had been noted previously, but again no angioid streaks. The multiple yellow and white dots were thought to be due to colloid bodies arising from the elastic membrane of Bruch.

The peripheral blood vessels revealed several abnormalities. No pulsation could be detected in either radial or ulnar artery or in the dorsalis pedis and posterior tibial arteries. Faint pulsation could be felt in an aberrant vessel in the midline of the flexor surface of both forearms just above the wrists. A loud systolic bruit was audible over both femoral arteries. This was loudest on the right side where a thrill could also be felt. Oscillometry revealed no pulsation in either leg below the knee. In spite of the absence of the peripheral pulses the hands and feet were warm and normal in colour. The blood pressure could not be recorded over the right brachial artery but was 120/70 mm. Hg in the left arm. Examination of the heart, lungs, abdomen and nervous system was normal. There were a few enlarged cervical lymph nodes, mainly on the left.

Haemoglobin was 74% with 3,670,000 red cells per c.mm. The white cell and platelet count, the bleeding and clotting time, and the capillary fragility test were again normal. A chest radiograph still showed the same uniform, miliary mottling in the left lung fields. A barium meal three weeks after the haematemesis was normal. A radiograph of the legs showed calcification in both femoral and popliteal arteries and a 2 in. shortening of the left tibia. Faint calcification was present in the axillary arteries. The serum calcium level was 10·5 mg. %, the inorganic phosphorus 3·1 mg. % and the alkaline phosphatase 13 units. Urinary examination and an electrocardiogram were normal.

He was treated by transfusion and discharged after three weeks. He remained well until September, 1950, when he had another attack of melaena for which he was treated at Hammersmith Hospital under Dr. J. G. Scadding. Gastroscopy by Dr. F. Avery Jones two weeks after the onset of melaena showed no abnormality in the oesophagus or stomach. Plethysmographic studies showed that the resting blood flow in the legs and arms was in the upper range of normal.

Family History. One brother, H.R., aged 25 when seen in University College Hospital in 1950, also gave a history of pain in the calves on rapid walking since childhood. The pain was relieved by standing still and never occurred when he walked at an ordinary pace. He gave no history of haematemesis or melaena. On examination he was found to have the skin changes of pseudoxanthoma elasticum on the abdominal wall, in the neck, axillae and groins. These changes had previously been noted when he was 11 years old. Biopsy at that time at The Hospital for Sick Children, Great Ormond Street, had confirmed the diagnosis of pseudoxanthoma elasticum. The fundi showed several white and yellow dots of the same type as those seen in G.R. and were thought to be due to colloid bodies. Angioid streaks were not seen. Neither the dorsalis pedis nor posterior tibial artery was palpable. Pulsation in the radial arteries could only be felt with difficulty. A systolic bruit was audible over both brachial arteries. The systolic blood pressure was 130 mm. Hg. The diastolic pressure could not be ascertained on account of the loud systolic bruit. Radiographs showed extensive calcification in both femoral arteries. A chest radiograph was normal.

Two sisters were said to be normal. Two other children had died in infancy, one of pneumonia and one of gastro-enteritis, and there had been one miscarriage. The mother was alive and well. The father had died of carcinoma of the bronchus. The parents were not consanguineous.

Discussion

This case supports the view that the skin condition of pseudoxanthoma elasticum is only one aspect of a more widespread disease of elastic tissue in which the eyes and the peripheral and gastro-intestinal blood vessels, and possibly those of other organs may also be involved. Although Carlborg (1944) has previously demonstrated diminished pulsation and calcification in the arteries of the limbs in patients with pseudoxanthoma elasticum, many of his subjects were over 40 and arteriosclerotic changes may have been responsible for some of his findings. In the case described, and in his brother, intermittent claudication had been present since early childhood. Calcification in the femoral arteries was clearly visible radiologically at the age of 9, and at the age of 14 no pulsation could be detected in the distal arteries of the arms or legs.

Carlborg (1944) considers that the reduction or loss of arterial pulsation in the limbs is not due to occlusion of the lumen but is a consequence of the degeneration and fragmentation of elastic tissue in the vessel wall. If the elastic tissue in the wall of a medium-sized artery degenerates, the arterial wall will mainly consist of smooth muscle and some connective tissue. Such a vessel is, in his opinion, unable to transmit pulsation normally even if the lumen is patent. The fact that in the present case the resting blood flow was normal, in spite of the absence of arterial pulsation, can be interpreted as supporting Carlborg's hypothesis. The alternative explanation is that there is some obliteration of the lumen and that the normal resting flow is the result of a well-developed anastomotic circulation. Biopsy of a non-pulsatile ulnar artery in a case of the

Grönblad-Strandberg syndrome (Scheie and Freeman, 1946) suggests that both factors may play a part. The lumen of the vessel was found to be smaller than normal but it was not occluded. There was thickening of the vessel wall due to hyperplasia of the muscular coat and the elastic tissue showed degeneration and fragmentation. In addition there was evidence of a well-developed anastomotic circulation.

The extensive calcification in the peripheral arteries presumably occurs as a secondary phenomenon in the areas in which the elastic tissue has degenerated. Calcification has also been observed in the affected areas of the skin (Finnerud and Nomland, 1937).

It appears reasonable to explain the recurrent gastro-intestinal haemorrhages in this and other cases by assuming that similar changes have occurred in the blood vessels of the gastro-intestinal tract as suggested previously by Carlborg (1944) and by Revell and Carey (1948). This assumption is supported by the fact that in the case described by Prick (1938) and Hagedoorn (1939), in which a terminal gastro-intestinal haemorrhage had occurred, tortuous, thickened vessels were found to be projecting into the lumen of the intestines at necropsy. Degeneration of elastic tissue and calcification could be demonstrated in the wall of these vessels.

It is much more difficult to account for the uniform miliary opacities which were demonstrated in the left lung fields of this patient. The appearances at first suggested the possibility of a previous lipiodol examination but no such investigation had ever been made. Miliary tuberculosis, sarcoidosis and lipoidosis can all be excluded on clinical grounds. The only record of changes in the lungs in association with pseudoxanthoma elasticum is found in a case reported by Balzer (1884). His patient had several haemoptyses and was found at necropsy to have cavities at the apices which were regarded as being due to fibro-caseous tuberculosis. On microscopy the elastic tissue in the alveolar walls of both lungs showed extensive degeneration and fragmentation similar to the changes found in the affected areas of the skin.

It is suggested that in our case the elastic tissue of the inter-alveolar septa and of the small pulmonary blood vessels has undergone similar degenerative changes. Such destruction of elastic tissue might lead to multiple small haemorrhages into the alveoli and the x-ray appearance might be due to the resultant haemosiderin deposits as in pulmonary haemosiderosis from other causes (Anspach, 1939; Scott, Park and Lendrum, 1947). In this connexion it is of interest that in idiopathic pulmonary haemosiderosis extensive damage of elastic tissue has frequently been found in the inter-alveolar septa and small pulmonary blood vessels and this has been regarded as the primary abnormality in this condition by several authors (Ceelen, 1931; Glanzmann and Walthard, 1941; Wyllie, Sheldon, Bodian and Barlow, 1948). Others, however, consider that the histological changes found in the elastic tissue are secondary to the deposition of the iron-containing pigment (Lendrum, Scott and Park, 1950). No case with symptoms of idiopathic pulmonary haemosiderosis has so far been described in which pseudoxanthoma elasticum, angioid streaks or abnormalities of the peripheral arteries have been observed.

The absence of haemoptyses in our patient does not necessarily rule out the possibility that the radiological changes in the lung are due to deposits of haemosiderin. Haemosiderosis of cardiac origin (Lendrum, Scott and Park, 1950) and idiopathic pulmonary haemosiderosis (Pilcher and Eitzen, 1944) have both been found in patients who had never had a haemoptysis. The main difficulty in accepting this, or any other explanation, of the miliary opacities observed is the fact that they are confined to one lung only. Their cause remains obscure.

Summary

The literature on the association of pseudoxanthoma elasticum with vascular abnormalities in the limbs and viscera is reviewed.

The case of a boy of 14 is described in whom pseudoxanthoma elasticum is associated with intermittent claudication since early childhood, absence of pulsation in the distal arteries of the limbs, calcification in the proximal arteries, recurrent haemorrhages into the gastro-intestinal tract, abnormalities in the fundi, miliary mottling in the left lung fields and unexplained shortening of one tibia. The patient's brother has also had intermittent claudication since childhood and in addition to pseudoxanthoma elasticum and changes in the fundi he has diminished pulsation in the distal arteries of the limbs and calcification in the femoral arteries at the age of 25.

This case supports the view that the skin condition of pseudoxanthoma elasticum is only one aspect of a more generalized, familial disease of elastic tissue in which Bruch's membrane of the choroid and the blood vessels of the limbs and viscera, including the lungs, may also be involved.

Our thanks are due to Dr. J. G. Scadding for permission to use his medical records, Dr. F. Avery Jones for the gastroscopy, Dr. M. Bodian for the original skin

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A CASE OF TRICUSPID ATRESIA WITH TRANSPOSITION OF THE GREAT VESSELS

BY

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Lack of development of the tricuspid valve is one of the rarer types of congenital heart disease. Before the advent of cardiac surgery it was of little more than academic interest, but now that such cases can be relieved surgically the condition assumes practical importance, and in cases of congenital heart disease every effort must be made to diagnose the anatomical defect.

Incidence

There is no trustworthy estimate of the incidence of congenital heart disease as a whole, still less of tricuspid atresia. Doubtless many infants have died with tricuspid atresia, on whom no post-mortem examination was made, with merely a diagnosis of congenital heart disease or even unrelated diagnoses, since many of them succumb to infections such as pneumonia, meningitis, septicaemia.

The first case to be recorded appears to be that of Sieveking (1854), and since then about 50 cases have been reported. Abbott (1936) found 16 cases of tricuspid atresia of developmental origin in her series of 1,000 cases of congenital heart disease. In 7,500 necropsies at the Philadelphia General Hospital, Szypulski (1937) found 111 patients with congenital heart disease, but not one of tricuspid atresia. Similarly, Rannels and Propst (1937) in 4,255 necropsies with 36 cases of congenital heart disease at the University Hospital of Pennsylvania found no case of this condition. Roberts (1937) gives an incidence of congenital heart disease of 1% in his series of necropsies, in which again there was no case of tricuspid atresia. However, Fell, Gasul, Davis and Casas (1949) had five cases of the disease out of 135 cases of congenital cardiac anomalies at the Cook County Hospital in 1938-39. More recently Rossi, Grob and Bettex (1950) had one case out of 81 cases of congenital heart disease between 1947 and 1949 in Zürich. Campbell (1948) found 10 cases in 187 cases of cyanotic heart disease, and has since reported five patients who have had successful subclavian-pulmonary anastomosis with great improvement. It appears then that the incidence of tricuspid atresia lies somewhere between 1 and 4% of all congenital heart disease.

Associated Defects

The most constant cardiac defect accompanying tricuspid atresia is hypoplasia of the right ventricle. Rarely this may be completely absent (Taussig, 1936; Eisenberg and Gibson, 1941). Some authors (Taussig, 1936; Cooley, Sloan, Hanlon and Bahnson, 1950) are of the opinion that this is the essential lesion and that the failure of valve formation is secondary. There must be a patent foramen ovale because of the absence of the right atrioventricular orifice. In addition, an interatrial septal defect may be present, and its extent determines whether the heart will be functionally bilocular or trilocular. There is often a severe malformation of the pulmonary vascular tract, usually atresia (seven out of Abbott's 16 cases), and then for the circulation to be compatible with life there must be a patent ductus arteriosus. Partial or complete transposition of the pulmonary artery and aorta occurs in some instances, and Robinson and Howard (1948) divide cases of tricuspid atresia into two groups according to whether or not transposition is present. They state that the majority are without this added anomaly. A patent interventricular septum is often present (14 out of Abbott's 16 cases). A case with dextrocardia and situs inversus has been reported by Waite (1950). Defects in other organs do not appear to be common, but a case described by Dustin-Henry and Dustin (1947) had agenesis of the right kidney. Bàrbera (1941) reported a case of a female pseudohermaphrodite infant 7 days old with multiple congenital defects in addition to the tricuspid atresia.

Aetiology

The condition is developmental in origin. Lewis (1945) stressed the importance of the microscopic

examination of the heart in cases with supposed foetal endocarditis and was of the opinion that probably many cases of congenital valvular defects had been incorrectly diagnosed as being of inflammatory nature.

A good deal has been written on the theory of the production of tricuspid atresia and transposition of the great vessels, and it is not proposed to consider this at length, since excellent reviews on the subject are available (Breslich, 1930; Bellet and Stewart, 1933; Lev and Saphir, 1937; Holder and Pick, 1939; Harris and Farber, 1939).

The first real contribution to the study of causation was that of Rauchfuss (1878) who thought that the developmental variety of tricuspid atresia was due to overgrowth and fusion of the endocardial cushions to the right of the interatrial septum. Manhoff and Howe (1945) were in agreement with this view. Vierordt (1898) was of the opinion that the condition was due to unequal division of the primitive atrium by a septum deviated too far to the right. Wieland (1914) and Mönckeberg (1924) supported this theory. Kühne (1906), however, postulated failure of the atrio-ventricular canal to shift enough to the right. Normally, the septum primum is directed towards the right margin of a single atrio-ventricular orifice, but the atrio-ventricular canal usually moves from left to right and so the free margin of the septum finally meets the lips of the orifice in the middle and gives the impulse to the endocardial cushions to fuse, with the production of two equally large canals. Spitzer (1923) developed a phylo-ontogenetic theory, in which the importance of torsion and haemodynamics was stressed. In his interpretation of Smetana's case (Smetana, 1929) he suggested that the tricuspid atresia was due to compression of the right venous ostium by a persistent bulbo-auricular crest and that the transposition of the great vessels was due to the inter-ventricular septum failing to rotate (Spitzer, 1929). Holder and Pick (1939), in reporting a case without transposition, point out that failure of the interventricular septum to rotate would result in narrowing and, finally, occlusion of the right venous ostium. This would also explain the existence of a patent interventricular septum, which is so commonly found in hearts with tricuspid atresia. For a detailed discussion of the embryology and aetiology of tricuspid atresia and transposition the reader is referred to the authors quoted above and to Keith (1909).

Clinical Findings

The main symptom is cyanosis, and some of the bluest babies seen with congenital heart disease are those with tricuspid atresia. Although many cases show cyanosis at birth, it is not uncommon for it to come on a few days later and to increase in the next few days, weeks or months. Sometimes cyanosis may be delayed for a month or two (Dustin-Henry and Dustin, 1947), up to a year (Soulié and Servelle, 1948), or even longer (Bellet and Stewart, 1933). Extremely rarely, cyanosis may be absent, usually due to the presence of transposition of the pulmonary artery and aorta (Hedinger, 1915). Characteristically the cyanosis is greatly increased by moving about, crying and feeding. It is interesting that Sieveking's (1854) original case did not show cyanosis until the day of death at 6 weeks of age. Since most of the patients are only a few months old, finger or toe clubbing is usually absent, but in older children it may be marked. Dyspnoeic attacks are a common feature. Cardiac murmurs may be present, but they are by no means constant. Their presence depends entirely on intra-cardiac pressure relationships and associated lesions, but, in spite of gross anatomical defects, murmurs may be absent. The liver and spleen may be enlarged and if the interatrial communication is small, the former will show presystolic pulsation (Waite, 1950). Vesell (1949) has described a sign in tricuspid stenosis which should theoretically be present in tricuspid atresia. This is the presence of a strong presystolic venous impulse over the jugular vein.

Diagnosis

In view of the success of surgical operations on the heart, the diagnosis of congenital heart lesions is now much more important. Tricuspid atresia is one which can be differentiated more easily than some, but as recently as 1936 no case had been diagnosed in life (Brown, 1936), but with the ancillary methods now at our disposal, few cases should go unrecognized. Fortunately, tricuspid atresia can be diagnosed in most instances without recourse to all of the modern methods of investigation, and only two will be considered here.

Radiology. The classical appearances in plain x-ray films of the chest are as follows according to Taussig (1936, 1947) and others. (1) The heart is rectangular or boot-shaped and makes a sharp angle with the sternum due to the absence of the shadow normally cast by the pulmonary conus, but the overall cardiac area is within normal limits. (2) The left side of the heart is greatly enlarged and the shadow is at right angles to the sternum. (3) There is a concave upper margin to the heart shadow. (4) The aortic arch is narrow and there is the appearance of a single vessel at the base of the heart. (5) In the left antero-oblique position, the right ventricle is small or indecipherable. With these findings, a diagnosis of tricuspid atresia may

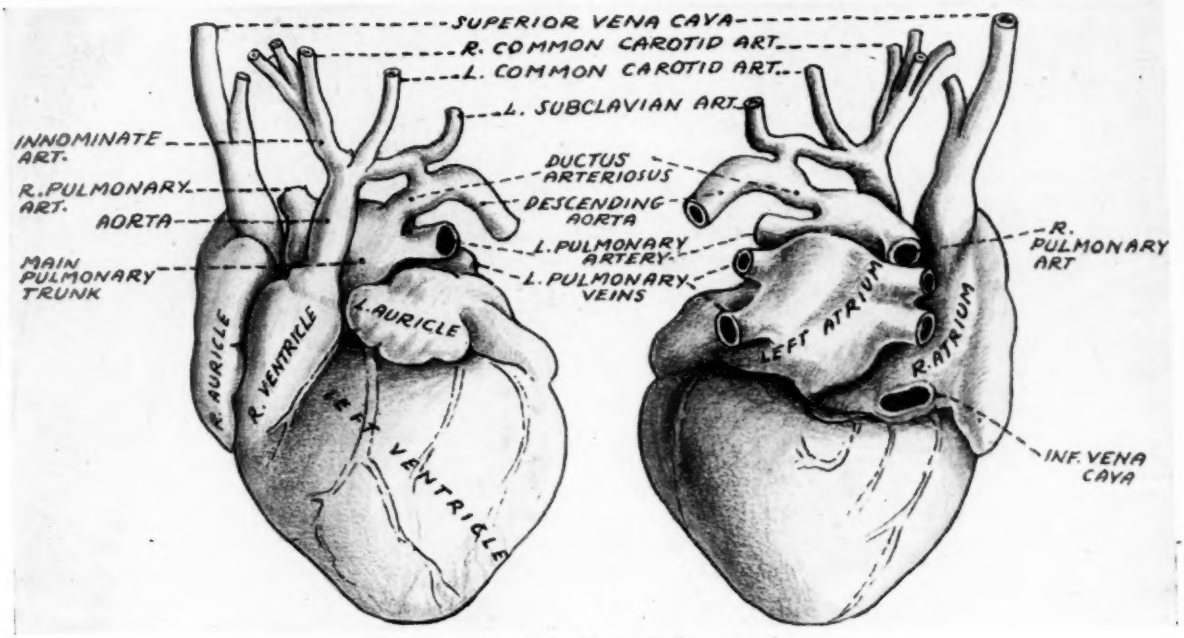

FIG. 1.—Drawing of heart before opening.

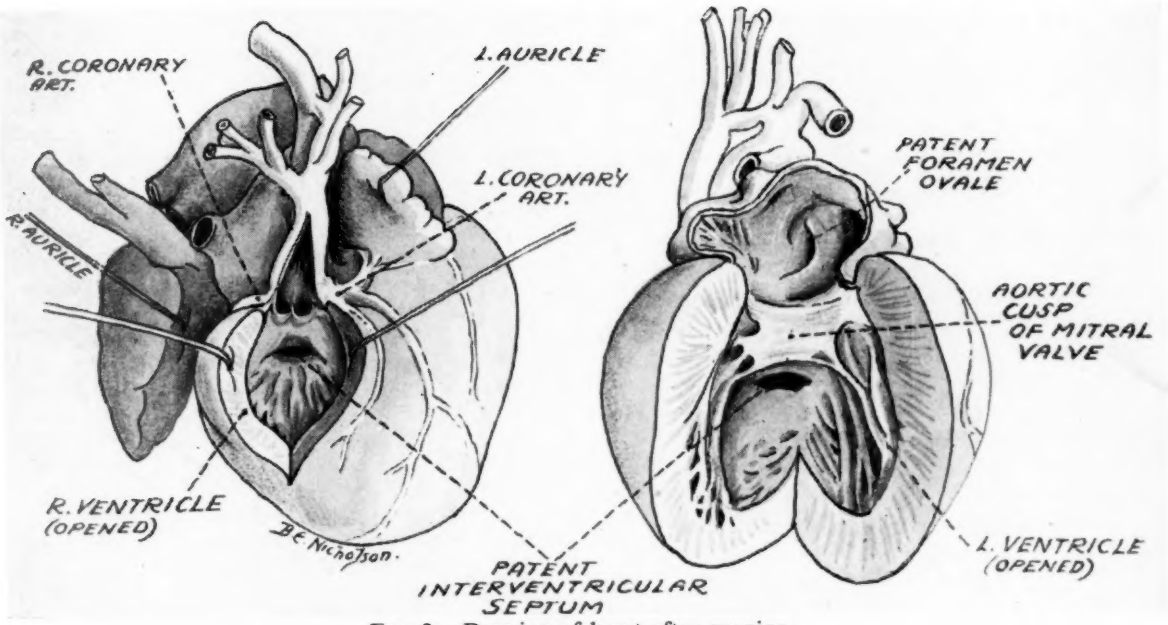

FIG. 2.—Drawing of heart after opening.

be strongly suspected, but Eisenberg and Gibson (1941) reported a case with an anomaly in which there was no concavity in the shadow of the area of the pulmonary conus. If cyanosis is mild, the co-existence of transposition of the great vessels is highly probable (Robinson and Howard, 1948). If surgery is to be considered, angiocardiography is a useful part of the radiological examination, for it evaluates the size of the interatrial communication on which the success of surgical procedures may depend. In a study of angiocardiography in congenital heart disease of the cyanotic type Cooley *et al.* (1950) stressed that this method of investigation does not distinguish between hypoplasia of the right ventricle alone and that associated with tricuspid atresia. They found two cases of right ventricular hypoplasia without the valvular defect. This is further evidence in support of the concept that the hypoplastic right ventricle is the fundamental abnormality and the atresia of the tricuspid valve a concomitant defect. Angiocardiography clarifies the impressions received from other data and also demonstrates anomalies of the great vessels. The typical appearances are shown in photographs by Wood (1950) and Gasul, Fell, Marino and Davis (1949). The main findings in the dextro-angiocardiogram in uncomplicated cases are no right ventricle, no pulmonary artery and filling of the left atrium and ventricle.

Electrocardiography. Most cases of cyanotic heart disease of congenital origin show right ventricular preponderance, but those with tricuspid atresia show a very definite left ventricular preponderance. This was first shown by Rihl, Terplan and Weiss (1929) although Papillon and Mourrut (1931) claimed priority in this respect. Statements that left axis deviation was pathognomonic of tricuspid atresia (e.g. Taussig, 1936; Miale, Millard, Beno and Custer, 1948) have been shown to be untrue by other workers. Schnitker (1940) found that 11 out of his 13 cases of Fallot's tetralogy had right ventricular preponderance, but Gasul *et al.* (1949) point out that left axis deviation can occur in Fallot's tetralogy with patent foramen ovale, and mention a case to be published in detail at a future date. In the presence of dextrocardia or gross conduction defects there may be a similar finding (Brown, 1936). Eisenberg and Gibson (1941) also say that left axis deviation is not incompatible with Fallot's tetralogy, particularly when this is complicated by other cardiac defects. In a study of 527 patients with morbus caeruleus Donzelot, Durand, Métianu and Vlad (1950) found 22 with left axis deviation, 18 of whom had tricuspid atresia. The others were two cases of uncertain diagnosis, one with pulmonary stenosis and partial transposition and one with coarctation of the aorta (infantile type). Since the right atrium is often hypertrophied, a high notched P wave may be an additional sign of value. In general, one should think of tricuspid atresia in a cyanosed child with left ventricular preponderance in the E.C.G. and a boot-shaped heart in the chest x-ray. The other, but rarer, condition in which left axis deviation is a feature is the infantile type of coarctation of the aorta. However, this is usually in children over two years of age, whereas tricuspid atresia is nearly always manifest much before this.

Prognosis

Without surgical treatment most of the patients with tricuspid atresia are dead within a year, though there are exceptions; for example, the cases of Smetana (1929); Moser (1936), Soulié and Servelle (1948) and one of those described by Cooley *et al.* (1950). Death occurs from cardiac insufficiency and may be sudden. In the pre-antibiotic era many patients died of infections. If transposition is present, this is beneficial and may enable life to be sustained for many years. Hedinger's patient (1915) lived to 56 without cardiac symptoms and died from an unrelated cause. If surgical intervention is possible, the prognosis is vastly improved, but it is too early yet to judge how successful will be the final outcome.

Case Report

J.F.S., a boy, was born on June 23, 1949, after a normal labour lasting 13 hours, and weighed 6 lb. 13 oz. There was no history of illness in the mother during the pregnancy, and her blood was Rh-positive (anti-D). Apart from marked physiological jaundice and some atelectasis the infant appeared normal until a week later, when his general condition became poor and periodic attacks of dyspnoea occurred. Some cyanosis of the extremities was noted at this time. Clinical examination revealed no abnormality in the chest apart from signs of non-expansion at the left base, but the liver was enlarged and hard, and the spleen was easily palpable. Four days later there were lung signs suggestive of bronchopneumonia, dyspnoeic attacks became more frequent, and cyanosis was marked. On July 7 the infant's condition showed some improvement, but on the following day he suddenly became deeply cyanosed and collapsed and died during a feed, at the age of 15 days.

Post-mortem Findings. External examination showed deep cyanosis of the lips and nail-beds. Icterus was not noticeable. The cord had separated and the umbilicus was normal. The testicles were impalpable. The body weight was 6 lb. 11 oz. (3·1 kg.).

There was no evidence of disease in the intracranial contents. The mouth and neck structures were normal. Each pleural cavity contained about 30 ml. (1 oz.) of clear, straw-coloured fluid. Both lungs showed patchy atelectasis, mostly basal, but no other abnormality. The heart weighed 45 g. and measured 42 mm. from apex to

base, and 50 mm. in its transverse diameter at the base. The right atrium and auricle were enlarged, and on opening them the muscle was seen to be much trabeculated and thickened (2·5 mm. average thickness). The foramen ovale was patent and measured 7 mm. in diameter, but no tricuspid orifice could be found. The endocardium was smooth and there was nothing to suggest an inflammatory condition in any part of the heart. The coronary sinus opened in the normal position and had a large valve. Examination of the great vessels showed complete transposition of the pulmonary artery and aorta, the latter arising from a rudimentary right ventricle (25 × 10 mm.) in the thickened muscle of the left ventricle. The first vessel to arise came off the aorta 2 cm. from the aortic valve, which was normal. The vessel was an innominate artery which then divided into the right subclavian and common carotid arteries. The next branch was the left common carotid, and just distal to this the aorta continued to the left and then divided to form the left subclavian artery and a very short, rather narrower vessel (ductus arteriosus). The pulmonary trunk arose from the left ventricle and was a large vessel 10 mm. in diameter, having a tricuspid semilunar valve at its orifice. It ascended for 15 mm. and then gave rise to three narrower vessels, two supplying the lungs, the right pulmonary artery being a continuation directly backwards and the left pulmonary artery proceeding obliquely to the left. The third vessel continued upwards to communicate with the aorta (ductus arteriosus). The diameter of the main vessel then slightly increased and continued downwards as the descending aorta (Fig. 1). The coronary arteries arose from the transposed aorta in their usual position, the left coronary running to the left in the groove between left auricle and left ventricle, with a large branch arising just outside the aorta and descending obliquely to the left across the anterior surface of the left ventricle. The right coronary ran downwards and backwards between the transposed pulmonary artery and upper portion of the right ventricle covered by the right auricular appendage, and gave rise to a number of branches descending the posterior surface of the left ventricle. On opening the left atrium, which was not enlarged, a normal mitral valve was visible, the orifice being 35 mm. in circumference. The left ventricle was enlarged (30 × 25 mm.) and thickened (8 mm.). The mitral orifice opened into the left half of the cavity, fully half of the latter being to the right of the aortic cusp of the mitral valve and opening into the transposed pulmonary trunk. Just below the pulmonary valve was a bridge of thick muscle below which was an opening 10 × 5 mm. communicating with the rudimentary right ventricle, i.e. a patent interventricular septum. The venous side of the heart appeared normal (Fig. 2).

In the abdomen the relevant findings were a grossly congested liver (140 g.) and spleen (11 g.); a large left kidney (24 g.) and a small right kidney (8 g.) showing hydronephrosis and hydro-ureter due to intramural constriction of the ureter in the bladder wall (Fig. 3).

HISTOLOGY. In the liver there was acute congestion, slight peri-portal fatty changes and scattered islets of haemopoiesis. Eosinophils were numerous in the portal tracts. There was acute congestion of the sinusoids and pulp of the spleen. Patchy atelectasis, capillary congestion and thickening of the arterioles due to an increase of muscle and elastic tissue in the media were seen in the lungs.

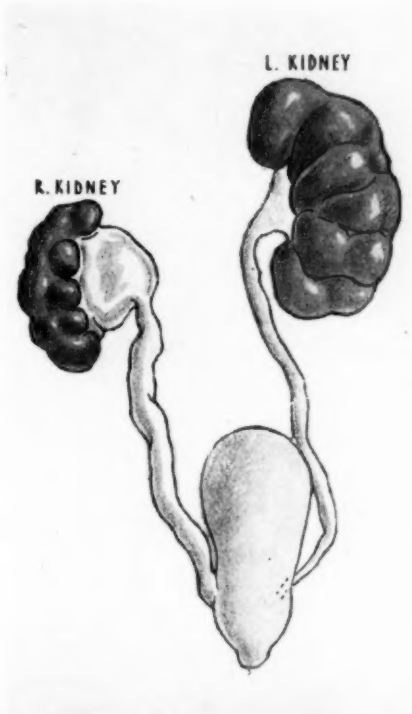

FIG. 3.—Drawing of kidneys, ureters and bladder.

Discussion

This heart showed many of the anatomical characters already reported in other cases of tricuspid atresia and is almost a replica of that described by Wason (1934). There can be no doubt that the condition was developmental, and it corresponds to Spitzer's type IV. The presence of a congenital stenosis of one ureter was probably coincidental. Clinically, the absence of heart murmurs rather suggested that the cyanosis was of respiratory origin, especially since signs of atelectasis were present. Had radiological and electrocardiographical examination been possible, it is likely that the diagnosis would have been manifest. Although mixing arterial and venous blood was occurring (Fig. 4), oxygenation was adequate except when the patient was moving about, crying or feeding. The existence of a small patent foramen ovale necessitated hypertrophy of the right atrium, and the left ventricle was large because it had to supply blood to the lungs as well as to provide the systemic circulation. It is not clear what caused the

attacks of dyspnoea. There was no evidence of left ventricular failure, and they may possibly have been of respiratory origin. Death appeared to have been due to acute congestive heart failure.

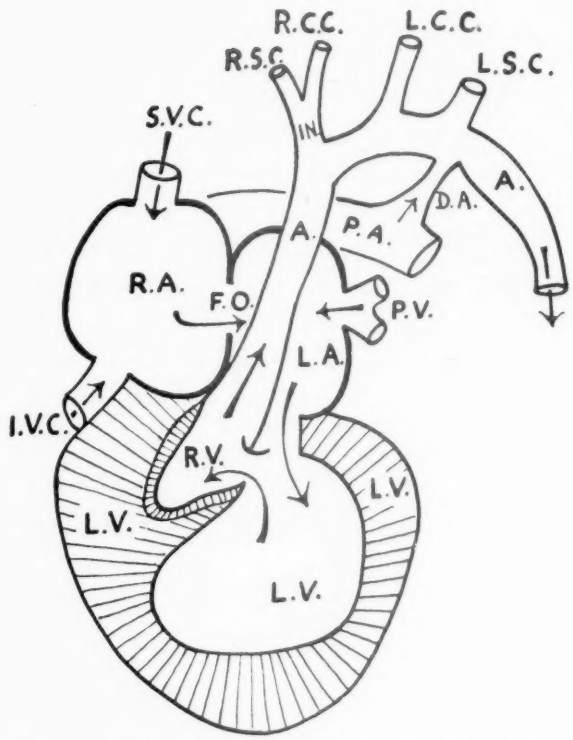

FIG. 4.—Diagrammatic sketch of heart to show the direction of the circulation.

S.V.C., superior vena cava: I.V.C., inferior vena cava; R.A., right atrium; F.O., patent foramen ovale; L.A., left atrium; P.V., pulmonary veins; L.V., left ventricle; R.V., right ventricle; A., aorta; I.N., innominate artery; R.S.C., right subclavian artery; R.C.C., right common carotid artery; L.C.C., left common carotid artery; L.S.C., left subclavian artery; P.A., pulmonary artery; D.A., patent ductus arteriosus.

Summary

A short account of the clinical and pathological manifestations of tricuspid atresia is given. Its diagnosis is discussed and a case reported with this condition with, in addition, complete transposition of the aorta and pulmonary artery.

I am grateful to Dr. Charles Pinckney for permission to publish this case. The drawings were executed by Miss B. E. Nicholson, to whom I tender my thanks.

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VENOUS THROMBOSIS IN ACUTE INFANTILE HEMIPLEGIA

BY

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Hemiplegia of sudden onset in children is not uncommon, and may occur in association with one of the acute infectious fevers, with a local infection such as mastoiditis or sinusitis, or in an apparently healthy child without obvious cause. Numerous series of cases have been published, one of the most important being that of Ford and Schaffer (1927) who collected 43 cases of acute hemiplegia, of which 16 followed acute infectious diseases, seven followed local infection, one was due to syphilis and 19 occurred in children considered to be healthy at the time of onset. The condition has aroused curiosity and much speculation during the past 70 years, and has been reviewed recently by Stewart (1948) and by Wyllie (1948).

Acute hemiplegia following local infection is due to cerebral venous thrombosis (Symonds, 1937 and 1940), and it is the purpose of this paper to show that many cases of acute hemiplegia in apparently healthy children are also due to this cause. Recent advances in the anticoagulant treatment of thrombosis appear to render such a review particularly apposite at the present time.

Clinical Picture

In a typical case a child under 6 years of age, who is well nourished and apparently in good health, suddenly develops a series of convulsions, and becomes unconscious for a period varying from a few hours to several days. As consciousness returns, it is found that the child has a hemiplegia, which is usually permanent to a greater or lesser degree. Sometimes there is a history of a slight upper respiratory infection, or of irritability for a day or two before the onset, but often the first convulsion occurs without warning. The convulsive movements vary from localized twitching of one arm to a generalized fit involving the whole body, and in a few cases in which the convulsions are more localized consciousness may not be lost. Occasionally there is a story of slight trauma before the onset, but such a history can be elicited about most children at any time, and its significance is difficult to assess. The hemiplegia usually improves in the weeks following the episode, especially in the lower limb, but only rarely clears up completely, and the child is often left mentally retarded, while epilepsy or involuntary movements are common at a later stage.

Present Series

Ten cases of acute hemiplegia have occurred in the medical wards of the Royal Hospital for Sick Children, Edinburgh, during the past 15 years and all survived the incident. None were associated with acute infectious fevers, as such cases are not normally admitted to this hospital. Eight of these 10 children had normal ear drums on inspection while two showed evidence of infection of the middle ear. These groups are not separated for reasons to be stated later.

Of these 10 cases, six were girls and four were boys, their ages ranging from 8 months to 5 years. All the children were well nourished, and four had a history of upper respiratory infection before the onset. Three cases had a history of trauma, one a slight blow on the head four months previously, the second a minor fall from a low chair a day before the first convulsion, and the third a slight blow on the head three days before the hemiplegia. No case had a history suggesting injury or anoxia at birth, and none was in any way retarded in early development.

The convulsions were confined to one side in three cases, involved both sides, but were most marked in the arms in three cases, and spread to involve the face, arm and leg in that order in two

TABLE I
CLINICAL SUMMARY OF TEN

Case	Age at Onset	Sex	Previous Health	Features of Onset
1	8 months	F.	Normal birth B.W. 7½ lb. No past illnesses	Slight cough and vomited three times; 36 hours later, right-sided convulsion
2	2 years, 4 months	M.	Normal birth B.W. 9 lb. Measles at 1 year	Anorexia, and vomited twice; sudden onset of twitching of right side on same day
3	1 year	F.	Normal birth B.W. 5¾ lb. No illnesses except chronic nasal discharge	Sudden paralysis of left arm, followed next day by paralysis of left leg; two days later, general convulsions
4	5 years, 3 months	M.	Normal birth Pertussis and chickenpox Minor head injury four months before	Sudden complete left hemiplegia No convulsive movements
5	1 year	F.	Normal birth B.W. 7 lb. Rubella at four months	Two days irritability, then twitching of left side of face, spreading to left arm and leg
6	1 year, 4 months	F.	Normal birth B.W. 7 lb. No illnesses	Two weeks irritability and coryza, sudden right-sided twitching. Recovered. 24 hours later, left-sided twitching
7	1 year, 10 months	M.	Normal birth B.W. 7 lb. No illnesses	Head cold. Six days later, vomited twice and had generalized convulsions, maximum in arms
8	10 months	F.	Normal birth B.W. 7½ lb. Bronchitis at 6 months	Sudden twitching of arms and mouth. Recovered but still drowsy. Two days later, generalized convulsion
9	1 year, 6 months	F.	Normal birth B.W. 7 lb. Bronchitis at 6 months	Fretful for two days, sudden twitching of right arm and leg, followed by loss of consciousness
10	2 years, 4 months	M.	Normal birth Twin Chickenpox, measles and pertussis	Respiratory infection three weeks previously. Four days irritability; minor blow on head three days before onset

cases. Two cases had sudden paralysis without convulsive movements. The hemiplegia was on the right side in five cases, and on the left in five cases. No changes were noted in the optic fundi except in one case which will be described in detail later.

The white blood cell count ranged from 8,000 to 33,000 per c.mm. The cerebrospinal fluid was under normal pressure in all cases, and its cell content varied from no cells to 100 per c.mm. The protein in the cerebrospinal fluid was raised to 85 mg. % in one case, was normal in eight, and was not estimated in one owing to contamination with blood. In all cases the fluid was sterile on culture.

After an average follow-up period of three years all the children had some residual signs of hemiplegia, and three showed some degree of mental retardation. Contrary to most reports, none has so far developed epilepsy, but the onset of this may be delayed for some years.

The main features of these 10 cases are summarized in Table 1.

TABLE I
SUMMARY OF TEN CASES

Findings on Admission	C.S.F.	Temperature	End-Results
Conscious; right hemiplegia; well nourished	No cells P. 85 mg. % S. 41 mg. % Ch. 648 mg. %	102·8° F.	One month later, still paralysed. Did not attend follow-up clinic.
Unconscious; twitching of right side, later right hemiplegia; well nourished	No cells P. 20 mg. % S. 94 mg. % Ch. 696 mg. %	105° F.	Ten years later, right hand still clumsy, leg almost normal. Average intelligence. No fits.
Conscious; left hemiplegia; well nourished	No cells P. 25 mg. % S. 35 mg. % Ch. 736 mg. %	98·4° F.	Eight years later, using left hand very little. Slight limp. Normal intelligence. No fits.
Conscious; left hemiplegia; well nourished	No cells P. 20 mg. % S. 68 mg. % Ch. 702 mg. %	98·8° F.	Six years later, still weakness of left arm and leg. Backward at school. No fits.
Unconscious; general convulsions, later left hemiplegia; well nourished	Blood-stained S. 71 mg. % Ch. 720 mg. %	106·4° F.	Three years later, left hand clumsy, occasional athetoid movements. Mentally normal. No fits.
Semi-conscious; left hemiplegia; well nourished	50 lymphocytes P. 28 mg. % S. 54 mg. % Ch. 770 mg. %	101° F.	Two years later, left hemiplegia only slightly improved. Mentally backward. No fits.
Unconscious; general spasticity, later left hemiplegia; well nourished	2 cells P. 28 mg. % S. 95 mg. % Ch. 720 mg. %	102·6° F.	Five months later, left arm can be moved, fingers clumsy. Mentally retarded. No fits.
Semi-conscious; right hemiplegia; well nourished	100 lymphocytes P. 25 mg. % S. 75 mg. % Ch. 730 mg. %	105·8° F.	Three months later, slight residual hemiplegia. Probably normal intelligence. No fits.
Unconscious; continuous right-sided convulsions; well nourished	4 lymphocytes P. 35 mg. % S. 150 mg. % Ch. 765 mg. %	105·6° F.	Eight months after onset, still marked weakness on right side. Normal mentally. No fits.
Semi-conscious; right hemiplegia and right homonymous hemianopia; well nourished	10 lymphocytes P. 21 mg. % S. 60 mg. % Ch. 715 mg. %	99·8° F.	Two months later, using left hand more than right. Hemianopia still present. Probably normal mentally. No fits.

Aetiology of the Condition

Various authors have speculated on the possible causes of acute infantile hemiplegia, but all have been handicapped by the fact that most patients survive, while those who die may do so in the acute stage when it cannot be certain that hemiplegia exists. Most of the necropsies reported have been carried out long after the onset of paralysis, and as Ford and Schaffer (1927) point out, little or nothing can be inferred from the end-results in such cases.

The theory that the condition is due to polioencephalitis (Strümpell, 1884) held sway for many years, but this hypothesis was based on clinical impressions and not on pathological evidence, and the virus of poliomyelitis has never been demonstrated.

Goodhart, quoted by Abercrombie (1887), suggested that the convulsions themselves might cause cerebral congestion and haemorrhage, but this has not been substantiated by necropsy evidence from other cases. Abercrombie himself suggested embolism, and though this may cause hemiplegia

in cases with heart disease, it seems an unlikely explanation in the majority of cases. Norman (1947) believes that birth injury plays some part in the pathogenesis, and that sufficient cortical tissue is spared to mask the original lesion for a time. This is not borne out by the cases presented in the present series, all of which had a normal birth history, the usual finding in these cases.

It is now widely held that many cases are due to vascular lesions, probably thrombotic in nature, and arterial rather than venous. Some authors have described changes in the arteries themselves, but although a few of these cases must be accepted, many are not convincing. For example, the often quoted case in which Ghetti (1909) described endarteritis, was a boy of 10 years, who already had a facial paralysis before his sudden hemiplegia and therefore hardly fits the conception of acute infantile hemiplegia. Ghetti himself thought that the condition was syphilitic, although he could not demonstrate the spirochaete. Most cases of cerebral endarteritis in infancy without hemiplegia have a previous history suggesting syphilis or meningitis, as in the case described by Altschul (1949).

Venous Thrombosis

Gowers (1888) suggested that the lesion might be thrombosis in a vein, and although this idea has not met with any general favour, more recent work lends support to his view. It was formerly held that extensive intracranial venous thrombosis would usually cause death, but it is now well known that patients with lateral sinus thrombosis frequently recover, and even extensive thrombosis of the superior longitudinal sinus may not be fatal (Ellis, 1937; Bailey and Hass, 1937a). Focal cerebral signs are known to occur dramatically without other indications of venous thrombosis, and such cases in the past have often been erroneously attributed to arterial thrombosis or to encephalitis (Symonds, 1940). In the few recorded cases of acute infantile hemiplegia where death has occurred in the acute stage most of the brains have shown gross vascular lesions, sometimes haemorrhage and sometimes softening, and no cause has been found for these appearances in the majority of instances (Stewart, 1948). The occurrence of softening secondary to venous thrombosis often results in haemorrhage, and Courville and Nielsen (1935) state that cortical venous thrombi may disappear after giving rise to gross changes in the brain.

In some cases a non-specific encephalopathy, such as occurs in infectious fevers, has been noted (Wyllie, 1948), and Putnam (1937) found that the acute lesion of venous thrombosis corresponds in all its details with that which is considered characteristic of encephalomyelitis following infectious diseases. Signs of obstruction of the lateral sinus need not be present, as it is not necessary for the thrombus to occlude the sinus to produce its effect (Symonds, 1937).

Any explanation of the cause of the hemiplegia must account for the observed maximum involvement of the upper limb, with convulsive movements frequently starting in the face, spreading to the hand and arm, and after an interval to the leg. Only a slowly extending lesion of the cerebral cortex could produce this ordered progression of localized convulsions, and followed as it usually is by a paralysis which only partly recovers, such a lesion is more likely to be venous thrombosis than anything else. The finding in other cases of convulsive movements on one side followed after an interval by movements on the other side, or of a gradual onset of convulsions spread over several days, makes it difficult to conceive of any process but venous thrombosis as a cause.

Merwarth (1942) and others consider that spread of thrombosis from the superior longitudinal sinus into the superficial middle cerebral vein (Rolandic vein) usually produces a characteristic initial involvement of the leg, with subsequent spread to the arm and finally to the hand which is least affected. However, Symonds (1940) pointed out that the pattern, while to be expected, is not constant, and Dowman (1926) described a case in which the reverse sequence of events took place. The following case would seem to bear out Merwarth's observations on the so-called Rolandic syndrome.

Case Demonstrating the "Rolandic Syndrome"

Case 11. A girl, aged 15 months, was admitted on January 7, 1951. Delivery had been spontaneous. Birth weight was 5½ lb. The infant thrived well, passing the milestones normally, and had no illnesses.

The infant was healthy until three days before admission, when the left foot suddenly began to twitch. Two hours later, the left arm began to twitch, and then the left side of the face. Seven hours after onset the child lost consciousness, and after a further six hours the right foot began to twitch, and the movements spread gradually up to involve the right arm and the right side of the face. Occasional twitches continued on both sides, but gradually diminished in frequency. She vomited just after the onset, but not again. Her temperature rose to 106° F.

On admission, she was seen to be a well nourished child, deeply unconscious. There was no increased tension of the anterior fontanelle, and the optic fundi were normal. The knee and ankle jerks were present and equal, the right plantar response was flexor and the left extensor. The abdominal reflexes were absent. Apart from occasional twitching of the right hand, no other abnormality was found in the nervous system.

The cerebrospinal fluid was not under pressure, and contained five lymphocytes and a few red cells per c.mm. The protein was 24 mg. %, the sugar 128 mg. % and the chlorides 890 mg. %. Culture was sterile. The white blood cell count was 31,000 per c.mm., and blood culture from the internal jugular vein was also sterile.

Death occurred a few hours after admission, and necropsy showed firm ante-mortem thrombosis of the superior longitudinal sinus and adjacent cortical veins, with more recent ante-mortem thrombus in both lateral sinuses, and some overlying subarachnoid haemorrhage. Both ears were healthy, and post-mortem cultures from ears and meninges were sterile. Microscopically, the walls of the veins were infiltrated by polymorphonuclear leucocytes, which were also numerous in the surrounding meninges and cortex (Fig. 1). Small collections of these cells were found in the liver, suggesting that infection was present, but no primary focus could be demonstrated.

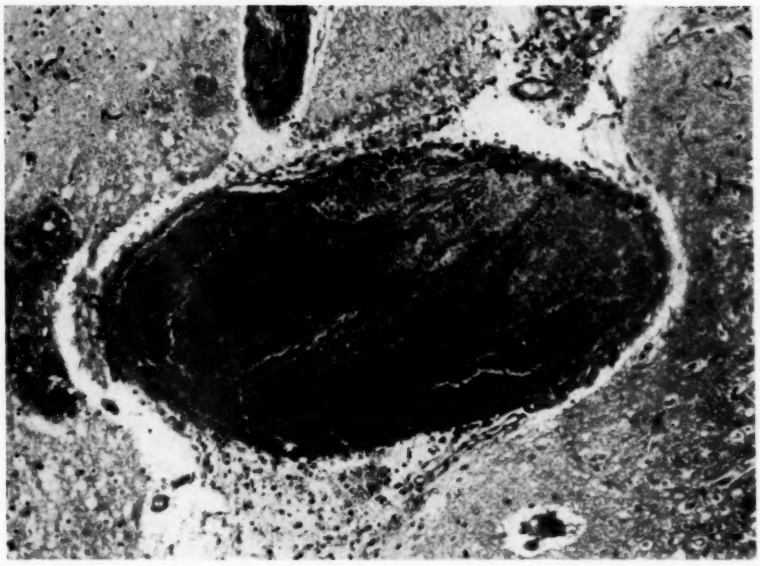

FIG. 1.—Photomicrograph of thrombosed cerebral vein (Case 11) showing polymorph infiltration of thrombus and surrounding tissues. H. and E. ×60.

It seems probable, therefore, that the reverse sequence of events observed in some cases of acute infantile hemiplegia could be explained by thrombosis spreading in the opposite direction. This might arise spontaneously in a cortical vein, as suggested by Gowers (1888), but there seems no valid reason why such a process should so consistently start in the cortical veins in the upper limb area of the motor cortex. A much more reasonable explanation is that in these cases the thrombosis spreads via the lateral sinus to the inferior anastomotic vein (vein of Labbé), which is frequently a wide channel. Courville and Nielsen (1935) described this mode of spread in discussing 23 cases of cerebral manifestations of otitis media, 17 of which showed paralysis affecting the arms before the legs and to a greater degree. They suggest that this mode of spread may occur only when the inferior anastomotic vein opens near the junction of the superior petrosal sinus with the lateral sinus, and not when it opens more caudally. These authors also point out that the chain of thrombosis need not be continuous, and that the process may spread through the lateral sinus to the cortical veins without extensive involvement of the sinus itself.

It has been thought that the onset of coma is caused by widespread circulatory disturbance of the cortex, due to extension of the thrombus to the torcular herophili (Salinger, 1923) or into the superior longitudinal sinus (Byers and Hass, 1933). Recent views on consciousness, however, suggest that global affections of consciousness are due to interference with the basal nuclear system, probably the anterior part of the corpus striatum in particular (Dandy, 1946). This could be produced by extension of the thrombosis into the internal cerebral veins, either by way of the straight sinus and the great vein of Galen, or by the cavernous sinus, but it could also be due to the effects of venous stasis, causing impairment of the circulation to the basal nuclei or their connexions. Campbell (1938) emphasized how little we know of the effects of venous stasis in the central nervous system, and that we should keep in mind the possibility of the occurrence of stasis of a reversible kind as a cause of parenchymal damage. Cortical venous thrombosis is usually accompanied by oedema which causes shift of the intracranial contents, and such anatomical derangements will also interfere with the basal nuclei, partly by affecting the circulation and partly by direct pressure.

Why a sudden paralysis should occur in some cases without convulsions is difficult to explain. Paralysis instead of convulsive movements has been noted in local epilepsy due to trauma, and Holmes (1927) considered that it was caused by primary inhibition instead of excitation of the cortical motor elements. It must also be remembered that, just as there is an inborn susceptibility to convulsions in epilepsy, so there may be individuals who are constitutionally resistant to convulsive agents. When the paralysis is permanent, as in acute

infantile hemiplegia, it may be due to a more rapid initial destruction of nervous elements than occurs in those cases which start with convulsions (Purdon Martin, 1944).

Two of the present series of cases presented unusual features which support the conception of venous thrombosis as a cause of acute infantile hemiplegia. They are therefore described in greater detail.

Cases Supporting Aetiology of Venous Thrombosis

Case 7. A boy, aged 1 year and 10 months, was admitted on October 31, 1950. Birth had been normal. Birth weight was 7 lb. The milestones had been passed normally, and the child had had no previous illnesses.

For one week before admission he had a slight coryza. Forty-eight hours before admission he lost his appetite, and on the same day he had a fall from a low chair with no obvious ill effects. He vomited twice next day, and had one loose stool. That night he had a series of convulsions, affecting principally the arms, and he was admitted to hospital unconscious, with a temperature of 102·6° F.

He was a well nourished child, with slight generalized spasticity of the limbs. The knee and ankle jerks were less brisk on the left side, and the plantar responses were equivocal. The optic fundi were normal. The ear drums were obscured by wax, but when this was removed they appeared normal.

The skull was normal radiologically, and the white blood cell count was 12,000 per c.mm. The cerebrospinal fluid was not under pressure, contained two cells per c.mm., with protein 28 mg. %, sugar 95 mg. %, and chlorides 720 mg. %.

FIG. 2a.—Thrombosed mastoid emissary vein in Case 7.

He had no further convulsions, but remained in a semi-conscious state. Next day his left arm was found to be weak, and on the following morning it was obvious that he had a left hemiplegia, with extensor plantar response on that side. He was treated with penicillin and streptomycin, and three days later it was noticed that the right mastoid emissary vein was firmly thrombosed (Fig. 2a). Treatment with heparin was started. He remained completely uninterested in his surroundings, but his general condition improved, and the paralysis gradually became less marked. By five weeks after the onset he could sit up but still seemed lacking in perception, not even recognizing his parents. During the next two weeks he made further progress, and was finally discharged seven weeks after onset. Three months later the left arm was still very weak and clumsy, and the leg was slightly weak, while he was still obviously mentally retarded. The thrombosed mastoid vein was still easily palpable. Fig. 2b shows the child five months after the onset of hemiplegia.

Case 8. A girl, aged 10 months, was admitted on November 22, 1950. Birth had been normal. Birth weight was 7½ lb. She thrived well until 60 hours before admission, when her arms and mouth suddenly began to twitch, and she became very limp. After a while the twitching stopped and the baby recovered a little, but during the next 24 hours she was drowsy and vomited several times. On the day before admission generalized convulsions started and continued until admission, when she was found to be semi-conscious, with a right hemiplegia.

FIG. 2b.—The child five months after the onset of hemiplegia.

The child's nutrition was good, and there was no increase of tension in the anterior fontanelle. The ear drums were normal. All limb reflexes were present, and no marked difference could be demonstrated between the two sides. The abdominal reflexes were absent.

The white blood cell count was 10,000 per c.mm. The cerebrospinal fluid was under normal pressure, and contained 100 lymphocytes per c.mm., with protein 25 mg. %, sugar 75 mg. % and chlorides 730 mg. %.

The left optic fundus (Fig. 3) showed a large haemorrhage almost obscuring the disc and extending temporally to the macula. The outline of the haemorrhage was irregular in shape, but the lower border was well defined and convex downwards, the appearance being fairly typical of pre-retinal bleeding. The arteries appeared normal, but the veins showed some congestion. There were also two or three small haemorrhages in relation to the veins above and nasal to the disc. The appearances were similar in the right fundus.

The child had several right-sided convulsions after admission, and then gradually recovered. Three months later she was still not using the right hand as much as the left, and tended to drag the right foot a little. She had no further fits, and appeared normal mentally.

FIG. 3.—Fundus of left eye in Case 8 (drawn by Dr. Maurice Paterson).

Case 7 showed many of the typical features of acute infantile hemiplegia. The history of a slight fall was only elicited by direct questioning, and was so slight that its significance in the aetiology is doubtful. The thrombosis in the mastoid emissary vein must almost certainly have spread from the lateral sinus. There was no sign of local sepsis.

In Case 8 the onset was rather prolonged, but otherwise typical. Dr. G. I. Scott, of the Eye Department, Royal Infirmary of Edinburgh, considered that the bleeding was certainly not due to local arterial or venous obstruction, and that the changes could only be explained by a sudden rise in venous pressure, as extensive subarachnoid haemorrhage was excluded by the results of lumbar puncture.

The mastoid emissary vein and the central vein of the retina form the two visible ends of an intracranial venous chain extending from the lateral sinus by the superior petrosal sinus to the cavernous sinus, and it is into this chain that the inferior anastomotic vein opens. In these two cases the thrombosis has presumably spread towards the ends of the chain, the mastoid and the retinal ends respectively. It is to be noted that neither of these cases showed the raised chlorides in the cerebrospinal fluid considered by Ebbs (1937) to be characteristic of thrombosis, but this is probably due to the greater severity of the process in his cases, for as Symonds (1937) has pointed out, in fatal cases there is usually very extensive occlusion of cerebral veins. The increased cell count in Case 8 is not unusual, as Symonds found that about half of the cases of hemiplegia following thrombophlebitis had a pleiocytosis in the cerebrospinal fluid.

Why should such a thrombosis occur in an apparently healthy child ? Thrombosis of the dural sinuses is usually described as being of two types, marantic and septic, the former occurring in ill, dehydrated children, and the latter showing all the signs of fulminating sepsis (Toomey and Hutt, 1949). In such circumstances, stasis and altered coagulability of the blood are likely to be of importance, but these factors must play a small part when, as in Case 11, focal cerebral signs are the first indication of disease. Infection may cause injury to vessel walls, possibly by the effects of bacterial products in the blood stream, and Case 11 shows that there may be no indication of the site of the original infection, even though there is post-mortem evidence that infection was present.

In Ebbs' series of 32 cases of cerebral sinus thrombosis in children every patient showed evidence of infection at necropsy, even when it was not demonstrable during life, and this was the only common factor (Ebbs, 1937). Beck and Russell (1946), in reviewing cases of aseptic thrombosis, were struck by the frequency of infective processes in some part of the body, and suggested that a possible mechanism was a localization of infection from a distant source by a process analogous with the Schwartzmann phenomenon. They were unable to reproduce this experimentally, however.

Thrombosis may occur in the veins in the course of infections of various sorts, but is not necessarily itself infected (Putnam and Alexander, 1938). The finding of inflammatory cells in the walls and perivascular tissues of thrombosed veins is not necessarily evidence of infection, and may occur in the absence of bacteria (Byers and Hass, 1933).

Pyrexia at the onset of acute infantile hemiplegia has been adduced as an indication of infection (Courville and Nielsen, 1935), but Bailey and Hass (1937b) have pointed out that dural sinus thrombosis itself is a cause of fever, possibly by interference with the central control of temperature regulation.

Role of Infection of the Upper Respiratory Tract

It is well known that thrombosis in the lateral sinus may follow otitis media and mastoiditis, but it may also be caused by naso-pharyngeal infection, however insignificant, and a latent period up to as long as four weeks may follow a tonsillar infection (Goldman, 1936; Maybaum, 1936). In reviewing past cases of acute infantile hemiplegia in apparently healthy children Courville and Nielsen (1935) were of the opinion that minor changes in the membrana tympani, now recognized as responsible for serious complications, may not have been mentioned owing

to under-estimation of their importance. Chronic inflammatory changes are not necessary in the bone and dura for invasion of the subdural spaces, and lateral sinus thrombosis can occur very early in acute otitis media, when clinical signs of the latter condition are minimal or absent. These authors emphasize that the often scarcely detectable and apparently insignificant changes in the drums must be considered as possible aetiological factors in manifest intracranial lesions, and have too often been ignored in the past. It is interesting to note that in one of their cases of hemiplegia with otitis cortical changes were found corresponding to those described by Ford and Schaffer (1927), which the latter authors ascribed to arterial thrombosis.

Cases 9 and 10 are examples of the type of case which Courville and Nielsen describe.

Cases Demonstrating Inflammatory Change as an Aetiological Factor

Case 9. A girl, aged 18 months, was admitted on March 5, 1950. Birth had been normal. Birth weight was 7 lb. The milestones were normal. She had bronchitis at 6 months; there were no other illnesses. She was healthy until two days before admission, when she became a little fretful, but otherwise seemed well. Three hours before admission the right arm and leg suddenly began to twitch, and she rapidly lost consciousness, her temperature rising to 105·6° F.

On admission she was seen to be a well nourished child, with continuous convulsive movements of the whole of the right side. Slightly indistinct edges were noted in the right optic disc, but these were not noted later. The right ear drum was normal, and the left was injected with loss of the light reflex. The white blood cell count was 33,000 per c.mm., and the cerebrospinal fluid contained 4 lymphocytes per c.mm., with protein 35 mg. %, sugar 150 mg. % and chlorides 765 mg. %.

Treatment was started with sulphamezathine, penicillin and streptomycin, and two days later heparin was added.

On the day after admission the movement stopped, but she was left with a right hemiparesis. A myringotomy was carried out on the left ear drum, but only a little muco-pus obtained.

Her general condition improved slowly, but two weeks after onset the hemiplegia was still almost complete. Physiotherapy was then started, with some improvement in function during the ensuing month, but eight months after onset the child still had marked weakness and incoordination on the right side.

Case 10. A boy, aged 2 years and 4 months, was admitted on January 29, 1951. Birth had been normal. He was a twin. Milestones were normal. He had had chickenpox, measles and pertussis.

He was well until three weeks before admission, when he developed a respiratory infection diagnosed as influenza. He recovered in a few days, but 10 days before admission the respiratory symptoms recurred, and one week later he became rather listless and lost his appetite. Three days before admission he banged his head, and though not very upset by this, he seemed rather drowsy next day. On the morning before admission paralysis of the right side of the face and the right arm developed, and a few hours later the right arm began to twitch and he became semi-conscious.

On admission, he was seen to be a well nourished child with marked weakness of the right arm and right side of the face, and slight weakness of the right leg. Apart from slight pinkness of the left ear drum, no other abnormality was found. His temperature was 99·8° F., and the white blood cell count was 21,000 per c.mm. The cerebrospinal fluid was not under pressure, and contained 10 lymphocytes per c.mm., and protein 21 mg. %, sugar 60 mg. % and chlorides 715 mg. %.

Treatment with sulphamezathine, aureomycin and heparin was started, and next day he was more conscious, and was noted to have aphasia and a right homonymous hemianopia. Six days after treatment was started the paralysis began to improve, but the aphasia and hemianopia remained complete. He was discharged three weeks after admission, and when seen one month later he had improved a great deal mentally, was saying a few words, and was using the right hand a little. The hemianopia, however, was still present.

Both these cases showed evidence of ear infection. In Case 9 there was definite left otitis media, but of recent origin and not severe, while in Case 10 there were only slight changes in the left drum.

In Case 10 there was also a history of slight trauma, and again it is difficult to be certain of the part this played in the aetiology, but as pointed out above, such a history is almost universal in small children. It is more than likely to have been coincidental, but the possibility that trauma of this mild type precipitates the thrombosis cannot be entirely excluded, as it is well known that more severe head injuries may cause sinus thrombosis (Purdon Martin, 1944).

The hemianopia noted in Case 10 is important, because it emphasizes that venous thrombosis may affect areas other than the motor cortex, in this case probably the optic radiations. Hemianopia was not noted in the other nine cases in this series, but it may well have been missed, as it is not always obvious in a young child unless especially looked for.

Treatment

In the past the majority of these cases have received only symptomatic treatment, with perhaps sedatives to control the fits. As minor infection may play a significant part in the pathogenesis, it would seem logical to administer full doses of the appropriate antibiotic from the start.

Since thrombosis has already occurred, anticoagulants cannot be used prophylactically in these cases, but they may be of value therapeutically in preventing further spread of thrombosis and possibly in dissolving the clot, as they have been shown to do

experimentally if given early enough (Rabinovitch and Pines, 1943). In addition reabsorption of oedema is hastened by heparin therapy (de Takats, 1950) and it is reasonable to suppose that heparin would produce the same beneficial effects in intracranial thrombosis as it does in deep venous thrombosis in the leg, where the subsidence of swelling is dramatic (Bauer, 1946).

Anticoagulants have been used in intracranial thrombosis since Goodhill (1944) first treated a case of cavernous sinus thrombosis with heparin, and where there is definite evidence of thrombosis as in Cases 7 and 8, heparin is undoubtedly indicated. The danger of anticoagulant treatment is intracranial haemorrhage, and this has been known to occur where dicoumarol has been used without proper safeguards (Shlevin and Lederer, 1944), but when carefully used the risk is not great (Hines and Barker, 1949) and is certainly justified in view of the poor prognosis as regards mental attainments and physical function. Evidence of haemorrhage accompanying thrombosis, such as xanthochromia or red cells in the cerebrospinal fluid, is not a contraindication to this treatment, but caution should be exercised in selecting patients, and where the diagnosis of thrombosis is in doubt, the exhibition of anticoagulants is unwarranted (Foley and Wright, 1950).

Heparin is preferred to dicoumarol in these cases because the effect is more easily controlled, while the difficulty of obtaining venous blood at frequent intervals from children (which is necessary since micro-analytical methods have proved unreliable) also contraindicates dicoumarol. In addition, heparin acts more rapidly and its effect ceases in a few hours, and, when properly used, the tendency to bleed seldom gives trouble (Jorpes, 1946).

Heparin was used in conjunction with antibiotics in Cases 7, 9 and 10, but it is not possible to draw any conclusions as to the efficacy of treatment from these few cases. Nevertheless, theoretical considerations would indicate that such is the treatment of choice, and a short experience of its use in the Department of Surgical Neurology in Edinburgh has provided convincing evidence of its importance and value in the management of cerebral venous thrombosis (Dott, 1951).

Conclusion

The division of cases of acute infantile hemiplegia into those who have an obvious local infection and those who are apparently healthy is artificial, as many of the latter group may have an aural or other upper respiratory infection with minimal or absent clinical signs. Venous thrombosis is the probable cause of the paralysis in many of these cases, and it may spread to the motor cortex from the lateral sinus by the inferior anastomotic vein, or from the superior longitudinal sinus by the superficial middle cerebral vein, the variation in the pathways and differing rate of spread accounting for the diversity of modes of onset.

Other areas of the brain may also be affected, as evidenced by impairment of sight or speech, and a careful search should always be made for such associated lesions.

The fact that arterial changes have been found in a few necropsies does not alter this conclusion, as rare cases with widespread arterial disease are the very cases in which the result is likely to be fatal, and it has been shown that recovery is common even after extensive intracranial venous thrombosis.

Treatment with anticoagulants and antibiotics is strongly indicated in view of the severe effects of the thrombosis.

Summary

Acute infantile hemiplegia is briefly described, and the findings in 10 cases noted. Two of these cases showed features pointing to intracranial venous thrombosis as a cause.

The cause and effect of intracranial venous thrombosis are discussed, and illustrative cases described.

It is concluded that venous thrombosis due to a minor upper respiratory infection may be the cause of many cases of this syndrome, and that division of cases into those with and those without obvious infection is unnecessary.

Treatment with anticoagulants and antibiotics is advised in those cases which are due to venous thrombosis.

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LOBSTEIN'S SYNDROME

BY

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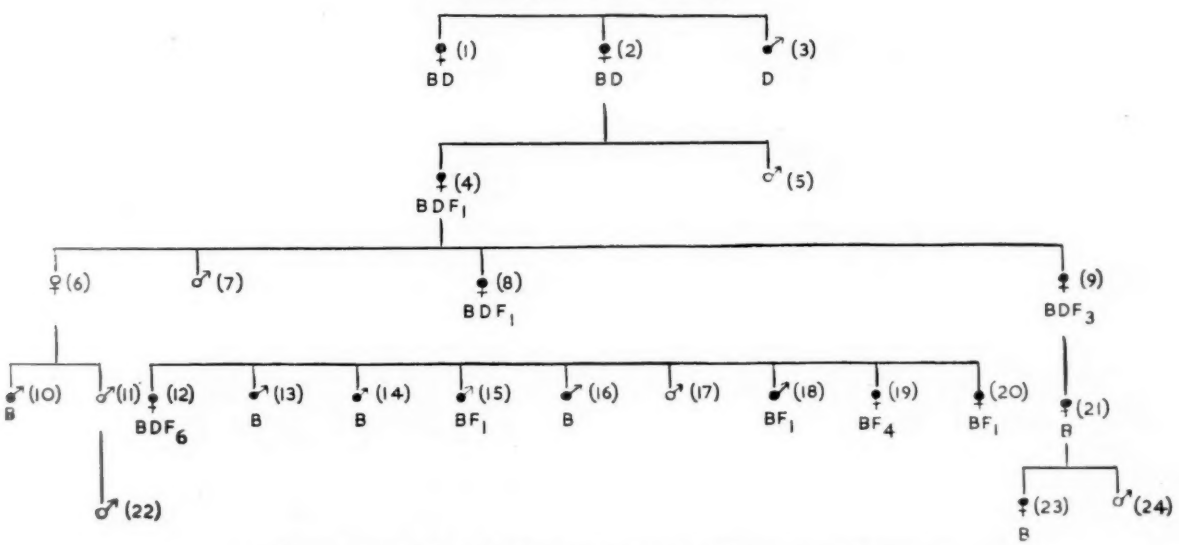
The purpose of this brief communication is to add a footnote to a paper published in this journal 19 years ago (Ottley, 1932) describing a family of which many members showed the hereditary condition named by Lobstein, who in 1833 gave the first account of it, osteopsathyrosis. The cardinal manifestations of Lobstein's syndrome are fragility of bones, blue coloration of the sclerae, and deafness (otosclerosis), occurring singly or in combination in affected members of certain families. Various subsidiary features have been described in some families, including malformation of the skull (*crâne à rebord*), precocious arcus senilis, laxity of ligaments, abnormal electrical reactions of the muscles, white patches in the nails, unusual fineness of the hair, and deficient formation of dental enamel.

The hypothesis that the condition originates in an inherited developmental defect of the mesoderm appears to have won general acceptance. The association with defects in tissues of other origin, e.g. in the enamel of the teeth, would, on this supposition, be merely fortuitous.

In the family under consideration the most striking feature is the tendency for the females to be more severely affected than the males. No male member is known to have exhibited the whole triad of cardinal signs. Since the date of my first paper, two members, numbers 9 and 21 (mother and daughter), have had operations for cystic mastitis, the mother on both breasts, the daughter on one,

TABLE I

Genealogical Tree of Family



B=blue sclerae; D=deafness; F=fractures (figure signifies numbers of fractures)

at the age of only 21. This daughter, now aged 23, shows a particularly well marked arcus senilis, most striking in so young a woman, and sclerae of a slatey blue. She has never had a fracture, but fractures are a less conspicuous feature in this family than in some of the families which have been reported. She has as yet no sign of otosclerosis. The mother, number 9 in Table 1, the genealogical tree brought up to date, had an operation for hallux valgus in 1937. The excised bone showed no histological abnormality. She is now stone deaf, able to hear nothing without a hearing apparatus and very little with it.

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PNEUMONIA AND EMPYEMA IN CHILDREN

BY

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From the Royal Edinburgh Hospital for Sick Children

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In 1929 McNeil, Macgregor and Alexander reported in this journal the results of a combined clinical and pathological investigation of pneumonia in childhood. Their report appeared 20 years after the publication of a paper by Dunlop (1908) based on the study of 500 cases of pneumonia treated in the same ward. The present communication records the results of an investigation of 369 cases of pneumonia and 19 cases of empyema treated in the same hospital in 1947, 1948 and 1949, and indicates such changes in these acute respiratory infections as can be ascertained from a comparison of the three series.

Material

The present series comprises all the cases of acute pneumonia admitted to the three medical wards of the Royal Edinburgh Hospital for Sick Children from April, 1947, to March, 1949, inclusive. The information required has been extracted from the ward records and the diagnoses are based on consideration of all the available data: history, clinical findings, radiographic appearances and pathological reports. The criterion for the diagnosis of pneumonia has been incontestable evidence of pulmonary infiltration. In 28 instances this was determined at necropsy, in 325 cases by radiography, and in the remaining 16 cases by clear-cut physical signs. Several cases registered as pneumonia in the casebooks have been omitted since the evidence was not sufficiently strong to support the diagnosis. On the other hand it is probable that some cases may have been missed, because of unavoidable delays in, for instance, x-ray examination. I think these are few, and that the series includes the great majority of the cases of pneumonia encountered in the wards in these years.

I do not intend to reopen the question of the diagnosis of the types of pneumonia in early childhood. The matter has been frequently, if rather inconclusively, discussed by many writers, and Wallace's (1937) comment that ' there is as yet no uniformity of opinion as to the criteria which distinguish bronchopneumonia from alveolar pneumonia in very young children ' is probably still true. Since the distinction must be attempted, however, in order to compare the different series, the principle has been adopted in dealing with the present material of regarding those cases of pneumonia which showed signs of a concomitant generalized bronchitis as being instances of bronchopneumonia, and those without such signs as cases of lobar pneumonia. This method of differentiation is based on the observation of McNeil, Macgregor and Alexander (1929) that in bronchopneumonia ' as a rule there is a generalized acute bronchitis affecting bronchi of all sizes throughout both lungs ', whereas ' in typical alveolar pneumonia the bronchial walls and the whole framework of the lungs are remarkably free from inflammatory infiltration '. No criterion will meet all possible objections, but this one appears to be, apart from post-mortem examination, the least objectionable. The results obtained from its employment are, as will be shown, in close agreement with those of other observers.

Results

There are three ways, on the information available, of comparing the present series with the earlier ones.

Incidence of the Types of Pneumonia. Of the 369 cases of pneumonia, 267 were diagnosed by the above standards as lobar pneumonia, and 102 as bronchopneumonia. Fig. 1 shows the number of admissions for each type by yearly groups. Fig. 2 shows the percentages of each type per year of age.

McNeil *et al.* discuss at some length the common belief that lobar pneumonia is rare under the age of 2 years, and give their reasons for thinking that this is not so. Table 1 shows the incidence of the types of pneumonia encountered in the two series in this age group. The agreement between the two series is close and indicates that the criteria utilized in the present investigation are valid. In 1939

TABLE 1

INCIDENCE OF LOBAR PNEUMONIA AND BRONCHOPNEUMONIA IN CHILDREN UNDER 2 YEARS OF AGE

	Lobar Pneumonia	Broncho-pneumonia
Present Series 0–1 year ..	41 (42·7%)	55 (57·3%)
0–2 years ..	87 (55·1%)	71 (44·9%)
McNeil *et al.* (1929) 0–1 year ..	43 (41·7%)	60 (59·3%)
0–2 years ..	143 (56·5%)	110 (43·5%)
Total 0–2 years ..	230 (56%)	181 (44%)

McNeil reported on 464 cases of pneumonia admitted to his ward in the 10 years following his first report. He gave the incidence of the two types of pneumonia in children under the age of 2 years in this second series as lobar pneumonia 133 (58%); bronchopneumonia 95 (42%). Thus in the three series, covering a period of nearly 30 years, from this one hospital, there is a fairly constant proportion of the two types of pneumonia in very young children. In all, 639 cases of pneumonia in children under the age of 2 years have been studied, and the distribution of the types in this not inconsiderable number is: lobar pneumonia, 56·8%; bronchopneumonia, 43·2%.

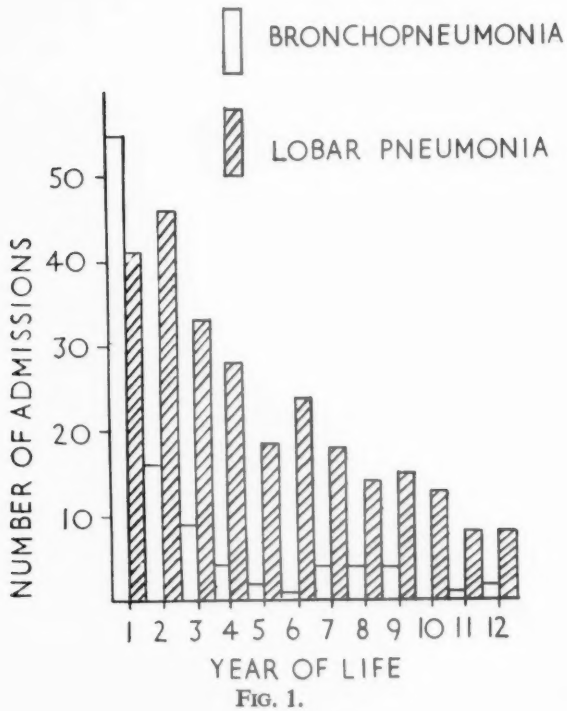

FIG. 1.

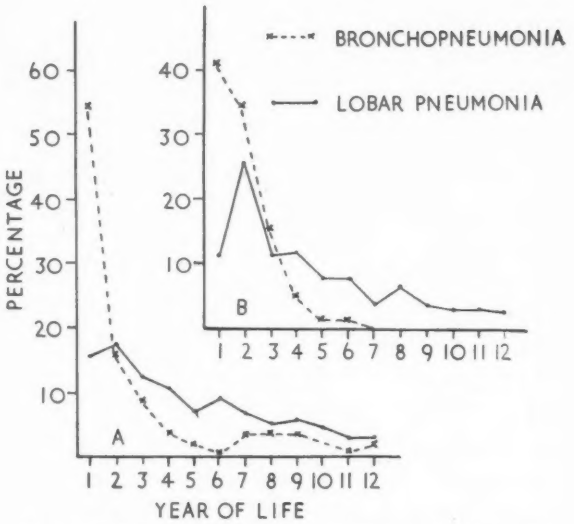

FIG. 2.—Diagram illustrating (A) present series, and (B) McNeil *et al.* (1929)

That these figures do not represent a local peculiarity, either of the diseases or of the standards of diagnosis, is indicated by Table 2 which gives details of two large series reported from America. The cases of primary pneumonia in children under 2 years of age were distributed as shown. It would appear reasonable to claim that between 50 and 60% of primary pneumonias in infancy are of the lobar type, and that this proportion has shown no appreciable change in Edinburgh over the past 30 years.

Dunlop's figures for his 1908 series are not comparable with those given above, since his cases of bronchopneumonia included a large number of infants who developed 'secondary' bronchopneumonia in the course of other illnesses such as

TABLE 2

INCIDENCE OF LOBAR PNEUMONIA AND BRONCHOPNEUMONIA IN CHILDREN IN U.S.A.

	Lobar Pneumonia	Broncho-pneumonia	Total
Nemir *et al.* (1936) ..	286	190	476
Bullowa and Greenbaum (1936) ..	264	255	519
Total	550 (55·3%)	445 (44·7%)	995

TABLE 3

MORTALITY RATES FOR LOBAR PNEUMONIA, BRONCHOPNEUMONIA AND BRONCHITIS IN CHILDREN ADMITTED TO THE ROYAL EDINBURGH HOSPITAL FOR SICK CHILDREN 1908-1949

Series	Lobar Pneumonia			Bronchopneumonia			Bronchitis		
	Total	Deaths	Mortality Rate	Total	Deaths	Mortality Rate	Total	Deaths	Mortality Rate
Dunlop (1908)									
0-2 yrs. 45	23	26·6%	233	57	24·5%	—	—	—	
2-12 yrs. ...102	3	2·9%	120	32	26·7%	—	—	—	
Total....147	15	10·2%	353	89	25·1%	—	—	—	
McNeil *et al.* (1929)									
0-2 yrs. 143	21	14·5%	110	67	61%	155	5	3%	
2-12 yrs. ...243	5	2·1%	34	11	32·4%	76	1	1·3%	
Total....386	26	6·5%	144	78	54%	231	6	2·5%	
McNeil (1939)									
*0-2 yrs.....133	11	8·3%	95	57	60%	—	—	—	
2-12 yrs. ...226	6	2·7%	10	4	40%	—	—	—	
Total....359	17	4·5%	105	61	59%	—	—	—	
Present Series									
0-2 yrs.....87	3	3·4%	71	26	36·6%	128	8	6·3%	
2-12 yrs. ...180	1	0·6%	31	4	12·9%	37	0	—	
Total....267	4	1·5%	102	30	29·4%	165	8	4·9%	

* Excluding infants under one month of age.

measles or typhoid. It is not possible to determine the number of cases of primary bronchopneumonia from the information given.

Mortality. Table 3 summarizes the data available for the four series reported from this hospital in the past 40 years. It is evident that there has been a constant decrease in the mortality from lobar pneumonia in the last four decades, until at the present day the mortality in children over the age of 2 years is negligible. (The single death recorded in the present series was of a girl of 11 who had in addition to pneumonia an extremely severe acute nephritis.) This decline in the mortality from lobar pneumonia has been commented on by many observers. Francis (1944), for example, has this to say :

> 'Over the past decade there has been a remarkable shift in the broad picture of pneumonia on this continent (North America) which has reached its culmination in the past five years. . . . About 1925 a decline in mortality from the disease began and was sharply accelerated between 1930 and 1937. . . . It appears that the decreasing mortality was to a large extent related to natural causes.'

Israel, Mitterling, and Flippin (1948) make a similar observation:

> 'Mortality from lobar pneumonia had declined sharply between 1925 and 1937, to a far greater degree than could have been due to the limited use of serum therapy.'

Both these reports refer to the further sharp decrease in the mortality of the disease since the introduction of chemotherapy. It may be concluded that lobar pneumonia, in common with a number of other diseases, e.g. scarlet fever, was, even before the discovery of the sulphonamides, undergoing a spontaneous and unexplained decrease in severity.

The wide discrepancy in the mortality rates for bronchopneumonia is rather disconcerting. The two series reported by McNeil are fairly consistent and show the disease to be a very serious one especially in infancy. It seems strange that the mortality in 1947-1949, with all the advantages of chemotherapy and oxygen therapy available in those years, should have been greater than in 1908, especially in view of the sevenfold reduction in

TABLE 4
INCIDENCE OF EMPYEMA IN TWO SERIES

Author	All Cases of Pneumonia + Empyema	Cases of Empyema	Incidence of Empyema
McNeil *et al.* ..	619	89	14·4%
Present series ..	394	25	6·3%

mortality of lobar pneumonia in the two periods. It may be unwise to speculate about this difference, but it seems possible, at least, that the early series included a number of cases which in the later series would have been diagnosed as bronchitis. This suggestion is not intended as a reflection on the diagnostic standards employed by Dunlop, but merely as a reminder that the more recent series have been examined radiographically, and the admittedly difficult differentiation of acute bronchitis from bronchopneumonia has been facilitated by the use of a technique not available to him. If, in the 1929 series of McNeil *et al.*, the figures for bronchitis and bronchopneumonia are combined, a total mortality rate of 22·4% is obtained. This is sufficiently close to the rate in the early series, 25·1%, to suggest that this explanation may have some validity. In the present series the mortality for the combined catarrhal infections is 14·2%. The reduction is much less striking than in the case of lobar pneumonia and, since there was no significant difference in the rates in the first three series, it may reasonably be attributed mainly to the use of chemotherapy.

Empyema. The 19 cases recorded here comprise all the children treated for empyema in the two years reviewed. Apart from these, there were six cases in which a purulent or sero-purulent exudate was found at necropsy.

Table 4 shows the incidence of empyema in the two series for which information is available. The decline in incidence is marked, and is comparable to that noticed by other writers. Chaplin (1947), for instance, found that after the introduction of sulphonamides the incidence of empyema in acute pneumonia (all types) in infants and children declined from 9·3% to 3·7%. This represents a decrease in incidence of 60% in the course of 10 years. The decrease in Edinburgh is of the same order.

Table 5 shows the results of the bacteriological examinations made in the two series. These results are in substantial agreement with other recently reported series (Forbes, 1946; Guthrie and Montgomery, 1947; Hipsley, 1949) in showing the remarkable decline in empyema due to pneumococci, and in the great increase in staphylococcal cases.

Discussion

From the data presented above it seems legitimate to conclude that (1) the types of pneumonia encountered in this hospital have remained fairly constant over the past 30 years, (2) lobar pneumonia has shown a progressive decrease in mortality since the beginning of the century, and (3) empyema is much less common than formerly and is now rarely due to pneumococci.

The last of these findings is almost certainly (compare Forbes, 1946) due to the employment of sulphonamides and penicillin, though exactly how they have produced this effect is uncertain. The large number of papers on staphylococcal pneumonia and empyema in children published in the past 10 years (for example, Clemens and Weens, 1942; Ladd and Swan, 1943; Riley, 1944; Philips and Kramer, 1945; Blumenthal and Neuhof, 1946; Watkins, Tichenor, Robb and Forbes, 1948; McLetchie, 1949) seems to indicate that staphylococcal infections of the lungs and pleura are not only relatively but absolutely more frequent than before the introduction of chemotherapy. This increase was already noticed before penicillin came

TABLE 5
RESULTS OF BACTERIOLOGICAL EXAMINATION IN TWO SERIES

	Organism Recovered			
Author	Pneumococcus	Streptococcus	Staphylococcus	Others and Mixed Infections
McNeil *et al.* ..	53 (76%)	7 (10%)	2 (3%)	8 (11%)
Present series ..	3 (14%)	3 (14%)	12 (55%)	4 (17%)

TABLE 6

DIAGNOSES ON ADMISSION TO HOSPITAL

Author	Total	Diagnosis on Admission		
		Pneumonia	Appendicitis	Meningitis
Adams and Berger (1922) .. 2–15 years ..	145	66 (45·5%)	25 (17·6%)	7 (4·8%)
Present series 2–12 years ..	93	37 (40%)	15 (16%)	4 (4·4%)

into general use and is not primarily related to the emergence of resistant strains of staphylococci.

The decline in the mortality from lobar pneumonia appears to be an instance of the spontaneous variation in severity of a disease, and though the rate of decline has become greater following the use of chemotherapeutic agents, its essential cause is unknown.

With regard to the constancy of the clinical picture presented by these diseases the following figures are of interest. In surveying the present series a note was made of the diagnosis with which each child was referred to hospital by the outside doctor. In 74% of the cases of acute lobar pneumonia this could be ascertained. In 1922 Adams and Berger published the result of an investigation designed to clarify the differential diagnosis of lobar pneumonia and acute appendicitis in children. They, also, noted the diagnoses with which their patients had been referred to hospital, or where there was no record of these, the diagnoses made in the admitting room. Table 6 shows the figures for the two series. The similarity is striking, and the conclusion seems justifiable that the disease in its early stages presented very much the same appearance in America in 1922 as it did in Scotland in 1947-49. It is of some interest to recall that Wells in 1889, after a most exhaustive review of the literature on pneumonia from Hippocrates onwards, came to the conclusion that ' there has been no actual change in the type of this disease, and that the pneumonic fever (lobar pneumonia) of today is that of our fathers and of past ages, and will be that of future generations '.

Summary

Data about the cases of acute respiratory infection admitted to the Royal Edinburgh Hospital for Sick Children from April, 1947, to March, 1949, are presented and compared with those available from earlier reports from this hospital.

The type of disease encountered does not appear to have changed appreciably in the past 30 years, and fairly constant proportions of the two principal types of pneumonia at various ages are shown to have been observed.

The mortality from lobar pneumonia has shown a steady decline from 1908 to 1949. This decline is largely unexplained.

Staphylococci have replaced pneumococci as the principal cause of acute empyema in this hospital. This change is related to, but not completely explained by, the introduction of chemotherapeutic drugs.

I am indebted to the physicians to the Hospital (Professor R. W. B. Ellis, Dr. D. N. Nicholson and Dr. J. L. Henderson) for permission to consult the records of their cases. I wish to thank Professor Ellis for advice about the presentation of this material.

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BOOK REVIEWS

Infant Feeding and Feeding Difficulties. By PHILIP EVANS and RONALD MAC KEITH. London: J. & A. Churchill Ltd. 64 plates. Pp. 255. Price 12*s.* 6*d.*

Here is an entirely new book which deals with the various aspects of feeding babies in health and sickness, and which approaches the subject in a somewhat different way from previous textbooks on infant feeding.

It contains a large amount of information set out in a way which makes it simple to read and easy to digest; the facts and figures relating to infant feeding, which everyone dealing with babies requires to know or to refer to occasionally, are all to be found in the text or in separate tables; appropriate references are given at the end of each chapter. It is, however, complementary to previous books on infant feeding which go into special aspects, such as artificial feeding in greater detail, and does not necessarily replace them in the library.

The authors are known to have a thorough knowledge of the needs of both the undergraduate and postgraduate student of today, and this is expressed not only in the simplicity of their explanations and of the methods they advocate but also in the easy and informal style of their writing. It is obvious from the comprehensiveness of the book that there is more in it than the medical student will require for his examinations, but there is very little in it that the doctor ought not to have read before he starts to practice.

The book is also notable for the thoughtful and moderate approach to the numerous problems of infant feeding, and the authors, who in the introduction apologize for their dogmatism, need hardly have done so.

The physiology of lactation and the preparation required for successful breast feeding before the birth of the child, together with an account of the technique of breast feeding and the troubles that may be met, are given full space and a clear exposition which is as welcome as it is likely to do a great deal of good in time to come. The causes of the common types of feeding difficulties are simply discussed, and it is unavoidable that this must be to some extent unsatisfactory to the person who wants an easy answer, because it is surely in the treatment of feeding difficulties in infancy that no book, however good, can take the place of personal experience and personal teaching.

The drawings with which the text is illustrated are clear and helpful, with the exception of the two showing the methods of splinting the limbs for intravenous therapy, in both of which the strapping is unsatisfactory. On the same subject the statement is made that in an ill-equipped hospital large instruments suitable for adults may be used for cutting down and inserting the cannula; it is this impression which still causes the failure of many such attempts throughout the country.

It is safe to say that this is a book which every young practitioner should read and which every young paediatrician will wish to possess, and there can be little doubt that it will become an established favourite in a very short time.

Disease in Infancy and Childhood. By RICHARD W. B. ELLIS. 1951. Edinburgh: E. and S. Livingstone. Pp. 695. Price 42*s.*

By delaying the writing of this review I have discovered how very readable this book is found to be by medical students; a good thing, for it is excellent in substance. Out of 695 pages, 200 deal with the diseases established before birth or in the first month of life, and though, when first turning over the pages, 120 of them on congenital malformations seemed a lot, the proportion is right.

The chapter on history-taking has a section of guidance in taking a psychiatric history which deserves a more general heading than ' Behaviour Problems ' for, as is pointed out, ' the child who is emotionally disturbed is likely to suffer in physical well being.' It is in dealing with difficult subjects in which organic and psychological factors are both concerned, that one most admires the balanced and helpful views concisely expounded. Diagnosis and treatment are both well done; success in the former will be helped by the many good illustrations and in the latter by the author's practical outlook, as for example in the suggested oxygen tent for premature babies.

The book is well printed; misprints are rare, perhaps ' bronchiectasis of the salivary ducts ' was one. A few errors of detail remain to be corrected, e.g. on BCG, and occasionally a superseded technique is recommended. Gore and Palmer's (1949) figures on the weight of children up to the age of 5 years should be given instead of the table quoted. Constipation in older children and incontinence of faeces deserve mention. Such minor criticisms can be made because the book is very good and will certainly have further editions.

GLYCOGEN DISEASE

BY

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Two Early Cases of Glycogen Disease

In June, 1928, at the meeting of the Dutch Paediatric Society, I read a paper on ' A Particular Disturbance in the Carbohydrate Metabolism in Childhood ', in which were reported observations on a boy whose metabolism showed peculiar disturbances. The mother had noticed that shortly after birth the baby's weight increased excessively and the abdomen became progressively larger. At the age of 8 months laparotomy was performed to determine the nature of the abdominal tumour. A very large, smooth liver was found but no biopsy was made.

In 1927, when the boy was 7 years old, I was able to make further investigations. At that time he was slightly stunted in growth, but much too heavy and gave the impression of a patient suffering from adiposogenital dystrophy. The liver was greatly enlarged; the spleen could not be felt. In the day specimen of urine, taken while the boy was on the ordinary hospital diet, neither sugar nor urobilin could ever be found, but acetone was often present. In a fasting condition the urine nearly always contained much acetone; in addition a considerable quantity of β-oxybutyric acid was frequently found. Radiographs of the bones of the hand revealed a severe delay in ossification (hepatic infantilism). Moreover, in the fasting condition marked hypoglycaemia was always present without any other abnormal symptoms. The mental development was normal. After the ingestion of 30 to 50 g. of glucose, fructose, or galactose sugar was never excreted in the urine, even when the test was repeated within a few hours. Ketonuria, present on fasting, often disappeared slowly during these tests. After the ingestion of glucose the blood sugar curve was biphasic. Further, it was found that after an adrenaline injection there was a slight elevation of the blood sugar, but simultaneously a markedly increased ketosis was noted and a decrease of the respiratory quotient. From this we concluded that the injection of adrenaline caused in this patient a markedly increased combustion of fat, probably because he was unable to react normally to the injection with a mobilization of glycogen. Finally the boy proved to be hypersensitive to very small quantities of insulin. For this reason and because of the presence of acetone in the urine it was thought that hyperinsulinism could be excluded. From these and other findings I concluded in 1927 that this was a condition, hitherto unknown, which showed an accumulation of carbohydrates in the liver and perhaps in the muscles in the form of glycogen, which could be mobilized only with great difficulty. Consequently the patient was constantly in a metabolic condition in which carbohydrates were difficult to mobilize. In this way the hypoglycaemia and the acetonuria could be explained, as well as the boy's preference for bread.

Just over a year after we published these conclusions the anatomical proof for our hypothesis was supplied by von Gierke (1929) and the chemical proof by Schonheimer (1929) in the necropsy findings on two children who, it had been recorded, during life also had had marked enlargement of the liver, but in whom hardly any metabolic examinations had been performed. In these children von Gierke (1929) found, apart from enlargement of the liver, enlarged kidneys, due to an accumulation of glycogen which could only be mobilized with great difficulty. On the basis of these findings he called this condition hepatomegalia glycogenica.

Pompe (1930) was the first to describe an enormous hypertrophy of the heart muscle due to glycogen accumulation, which he called cardiomegalia glycogenica.

It was several years before similar clinical and pathological descriptions penetrated into the literature of other countries. In 1933, at the third international paediatric congress in London, three

brothers were demonstrated suffering from cirrhosis of the liver without enlargement of the spleen. On this occasion I doubted this diagnosis and thought that probably in all three cases a glycogen liver was present, and as such the cases were later described.

In 1932 I observed a second case, a girl, then 5 years old; at the clinical and metabolic examination she showed features which corresponded with those found in the boy.

In 1933, after the researches of Cori and Cori (1931), we were able to obtain a better insight into the abnormal behaviour of both our patients with regard to their reaction to the injection of adrenalin. The absence of an initial blood sugar elevation after the injection was particular evidence of the immobilization of glycogen in the liver. The absence of the normal elevation of the lactic acid content in the blood, which occurs after the injection of adrenalin indicated an insufficient mechanism for mobilizing muscle glycogen, according to Cori and Cori (1931) and confirmed by Stetten (1946). Other metabolic disorders found at that time in both our patients were raised blood glycogen and hypercholesterinaemia. Discussing the differential diagnosis, the case described by Parnas and Wagner (1922) was referred to. Their patient showed a marked hypoglycaemia on fasting, without any symptoms, but always accompanied by acetonuria. The liver was enormously enlarged and the child showed symptoms of endocrine disturbance. In this case Parnas and Wagner (1922) had observed that, after the ingestion of various sugars there was hyperglycaemia and glycosuria with disappearance of the ketonuria, and for these and other reasons Parnas and Wagner (1922) assumed that in their case the liver no longer was able to convert sugar into glycogen. Later this patient developed into a case of diabetes mellitus. The possibility of cirrhosis of the liver and of a fatty liver, and of the syndrome of Mauriac (1930) had also to be considered in our cases. Arguments against the diagnosis of cirrhosis of the liver were particularly the absence of an enlarged spleen in both our patients and the fact that various liver function tests showed no abnormalities. The urine of the second case (the girl) showed a weakly positive urobilin reaction which appeared to indicate that the liver, in addition to glycogen accumulation, showed slight cirrhotic changes.

Kramer, Grayzel and Solomon (1935) were the first to indicate the possibility that a greatly enlarged liver combined with certain metabolic disorders might also be caused by a marked fatty infiltration of the liver. One of their cases showed a greatly enlarged liver, marked hypoglycaemia and no increase of the blood sugar after adrenalin injection. In this case, however, the hypercholesterinaemia and the ketonuria were absent, an absence which, with that of glycosuria after the ingestion of a large quantity of carbohydrates, indicated that the patient of Kramer *et al.* (1935) was able to utilize sugar.

Both our patients showed a complex of symptoms which differed from the symptoms observed in other patients with chronic disease of the liver. This conception was supported by the description of some cases of glycogen liver disease in which the diagnosis had been confirmed by necropsy or by biopsy in which a clinical and biochemical picture was found that was practically identical with that of both our patients. Since then some cases of cirrhosis of the liver in children have been described where some of the symptoms of glycogen liver disease were present. However, the presence of an enlarged spleen militated against the diagnosis of glycogen liver disease; moreover, at necropsy in some of these cases the liver proved to contain hardly any glycogen.

Differential Diagnosis

As dissociation of the disturbances in the liver function is well known, we could expect that the series of cases of glycogen liver disease described in the literature, would show a varying intensity of some of the symptoms. And indeed, this could be seen during the further observation of both our patients and in certain others also. The pathological picture is not always the same, and the quantity of fat or connective tissue, which is stored with glycogen, shows variations; for example, much fat was present in the first case of von Gierke (1929) and in the cases of Krakower (1936). (Here it is useful to recall the name *hépatomégalies polycoriques* proposed by Debré (1947) as a general name for an enlargement of the liver caused by an accumulation of glycogen or fat, or of both substances.) In our first patient the parents were consanguineous, a feature which has been observed by others in cases of glycogen disease. Moreover frequently more than one case of glycogen liver disease (or glycogen heart) has been observed in the same family (Abramson and Kurtz, 1946).

As to the differentiation between glycogen liver disease and the syndrome of Mauriac (1930) we must stress the fact that this syndrome is frequently found in children with diabetes mellitus some months or years after the beginning of insulin treatment. Some years ago Houet (1947) reviewed 28 cases from the literature and two observed by himself. This syndrome is characterized by arrest of growth, hepatomegaly with swelling of the

abdomen but without splenomegaly and ascites. For the differential diagnosis of glycogen liver disease the history is very important, but certain differences exist between the biochemical symptoms in both conditions.

The first clinical and pathological description of glycogen disease was followed by a large number of cases, mostly of hepatomegalia glycogenica, and some cases of cardiomegalia glycogenica. Besides this we find a number of cases with enlargement of more than one organ, due to accumulation of glycogen. We have already demonstrated that metabolic disturbances are found only in the hepatic form of the disease. In differentiating between this and other forms of glycogen disease (especially enlargement of the heart due to an accumulation of glycogen) a biopsy of the muscle can be of help, as the fibres of the striated muscles show a characteristic vacuolar structure without general enlargement.

Cardiomegalic Glycogen Disease

Wagner (1947) has recently described an increased glycogen content of the leucocytes in glycogen liver disease, a finding which should help greatly in diagnosis.

The diagnostic difficulties in the recognition of the cardiomegalic type of glycogen disease are much greater than in those of the hepatomegalic type. In the hepatomegalic form the disturbance of hepatic glycogenesis and glycogenolysis is responsible for an important part of the biochemical findings. As far as can be ascertained, these laboratory findings are absent in cases of cardiomegalia glycogenica, but it is probable that there is one common cause for the storage of glycogen in heart and liver. One of the arguments in favour of this hypothesis is that in both forms of the disease the accumulation of glycogen is not restricted to the organ which shows a visible enlargement, though in cases of hepatomegalia glycogenica the enlargement of the liver is predominant, and in cardiomegalia glycogenica, the heart enlargement. In the cardiomegalic type the accumulation of glycogen in the striated muscles is stressed, and they are sometimes equally enlarged. At present no other diagnostic test is available by which cardiomegalia glycogenica can be diagnosed during life, and in doubtful cases we have to rely upon the appearance at biopsy of the vacuolar structure of the skeletal muscle fibres.

Though less frequently than in the hepatomegalic form, more than one case of the cardiomegalic type of glycogen disease occasionally occurs in one family.

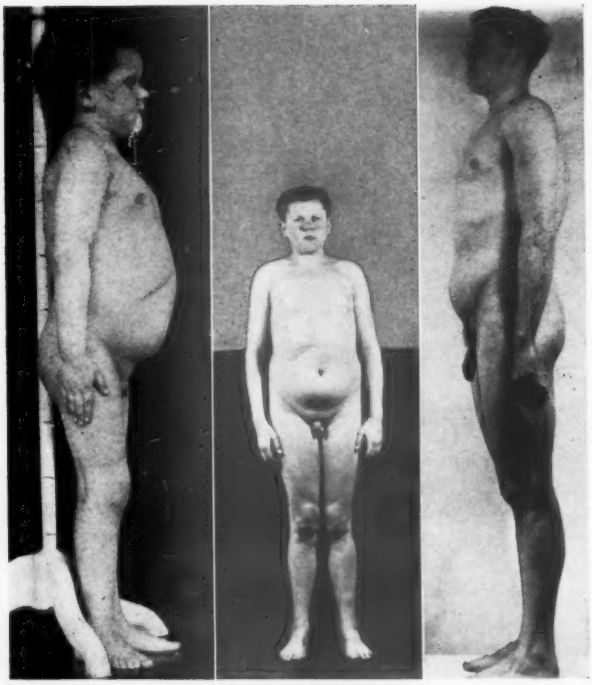
The clinical symptoms observed in a number of cases have already been mentioned in an earlier paper (van Creveld, 1939). In nearly all cases of glycogen heart disease diagnosed with certainty the children died between the ages of 4 months and 1 year, some of them earlier. This has remained constant, as appears from publications of Giampalmo (1944, 1949) and of di Sant 'Agnese, Andersen and Mason (1950).

The diagnosis of glycogen heart disease can be made only on certain limited clinical, pathological and chemical data. The clinical symptoms are few. The cases are nearly always young babies who do not thrive, show attacks of dyspnoea and sometimes of cyanosis during feeding. In some cases the dyspnoea and cyanosis have occurred suddenly, shortly before death. Physical examination usually shows the heart to be grossly enlarged, and the heart sounds to be normal. Sometimes there is a soft systolic murmur at the apex. The liver shows no or only a slight enlargement, although the spleen is sometimes palpable. In various cases impaired percussion with increased bronchophony and rhonchi were heard, especially over the left part of the thorax. The immediate cause of death is always acute heart failure, usually complicated by bronchopneumonia.

In antero-posterior radiographs the heart has been seen to be greatly enlarged in all directions, accompanied by signs of pulmonary collapse or emphysema. Electrocardiograms are of little use for the diagnosis of cardiomegalia glycogenica. Since the first description by Pompe (1930) little has been added to the pathological characteristics of the glycogen heart disease.

Follow-up of the Two Early Cases

Both our children are now grown up, aged respectively 30 and 24 years. Neither physical nor their mental development is retarded. The first patient is a well developed muscular man who shows no physical abnormalities. His height is now (July, 1951) 183 cm., his weight 89 kg. The urine and blood pressure are normal. He has been married for some years and has a son, about 1 year old, who seems to be perfectly normal. In the girl, who is married now, menstruation and secondary sexual development appeared at the normal time. She shows no physical abnormalities and is also well developed (in July, 1951, her height was 167 cm., weight 65 kg.). Some months ago she had an abortion, but we were unable to obtain further information about this. In both cases the liver is only just palpable, and has decreased in size since puberty (Fig. 1). Until he was 18 years old all the teeth of the boy were still deciduous, when gradually they were exchanged for permanent



1928 1938 1948

FIG. 1.—Photographs showing decrease in the size of the liver in our patient.

ones. In the girl the second dentition began at the normal time. On her first examination, when she was 5 years old, ossification was delayed, but in the course of some years this delay has disappeared, perhaps as a result of the anti-ketogenic diet which was prescribed at that time. In the boy the delay in ossification disappeared sooner; moreover for several years he has had a slight general osteoporosis.

Some authors are of the opinion that patients with glycogen liver disease show a special sensitivity to infections, but we have not seen this in our two patients.

In the course of years the biochemical symptoms of our patients have been studied at intervals. For many years we tried to influence the carbohydrate metabolism in the first patient, especially by prescribing a diet poor in fat and rich in carbohydrates. The general outlook of the young man has changed but little during and after puberty, and he has never shown alarming symptoms. His pronounced preference for bread has persisted for many years. After taking an extra quantity of sugar the urine never contained any glucose. The epiphyseal lines showed delayed fusion. The fasting blood sugar, which used to be extremely low, has increased in the course of years and for many years the fasting ketosis has disappeared.

In 1948 we performed some laboratory examinations (Table 1). The serum cholesterol and the blood glycogen levels were both slightly elevated. The fasting blood sugar was rather low and adrenalin injection was not followed by an increase of the blood sugar nor of the lactic acid, and only a slight acetonuria was present. Formerly after adrenalin injection the absence of an increased blood sugar was always accompanied by a marked increase in the ketosis.

In July, 1951, we once more examined his reaction to the adrenalin injection. First the blood sugar, lactic acid and cholesterol were determined in venous blood on fasting, and then the changes in blood sugar and lactic acid after the subcutaneous injection of 0·6 mg. of adrenalin were observed. These results and those of the examination of the urine are summarized in Table 1. The fasting blood sugar content was now practically normal but did not change after adrenalin injection. The urine in the fasting condition did not contain acetone, but two hours after the adrenalin injection the acetone reaction was slightly positive. The lactic acid content of the blood showed a slight, temporary rise, and the serum cholesterol was only slightly elevated.

Two years ago, at appendicectomy, the muscle fibres in the wall of the removed appendix (Fig. 2) proved to contain large quantities of glycogen (stained according to Best by Dr. R. van Dam).

In the girl the most striking feature is the decreased size of the abdomen. Her mental and physical development are normal. The decrease in size of the liver has been gradual, as can be seen in Fig. 3.

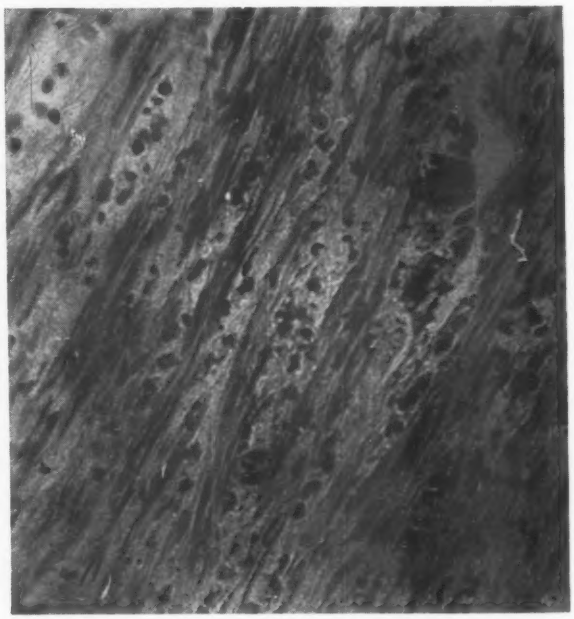


FIG. 2.—Section of wall of appendix showing glycogen in muscle fibres.

TABLE 1
HEPATOMEGALIA GLYCOGENICA IN CASE 1

	1948	1951
Height (cm.)	183	183
Weight (kg.)	—	89
Cephalin flocculation test	slightly +	
Takata-Ara test	—	
Cholesterol level (mg.%)	272	233
Blood glycogen level (mg.%)	19·5	

Blood and urine analyses	After 0·5 ml. adrenalin 1/1000 (1948)					After 0·6 ml. adrenalin 1/1000 (1951)				
			Urine					Urine		
	Blood Sugar (mg.%)	Lactic Acid (mg.%)	Acetone	Glucose	Diacetic Acid	Blood Sugar (mg.%)	Lactic Acid (mg.%)	Acetone	Glucose	Diacetic Acid
Fasting	68	20	—	—		92	19	—	—	—
after 10 min. ..	69	—				89	23			
„ 20 „ ..	68	—				95	23			
„ 30 „ ..	68	20	—	—		95	20			
„ 60 „ ..	66	17				95	20	—	—	—
„ 90 „ ..						95	21			
„ 120 „ ..	55	18	+	—				—	—	—

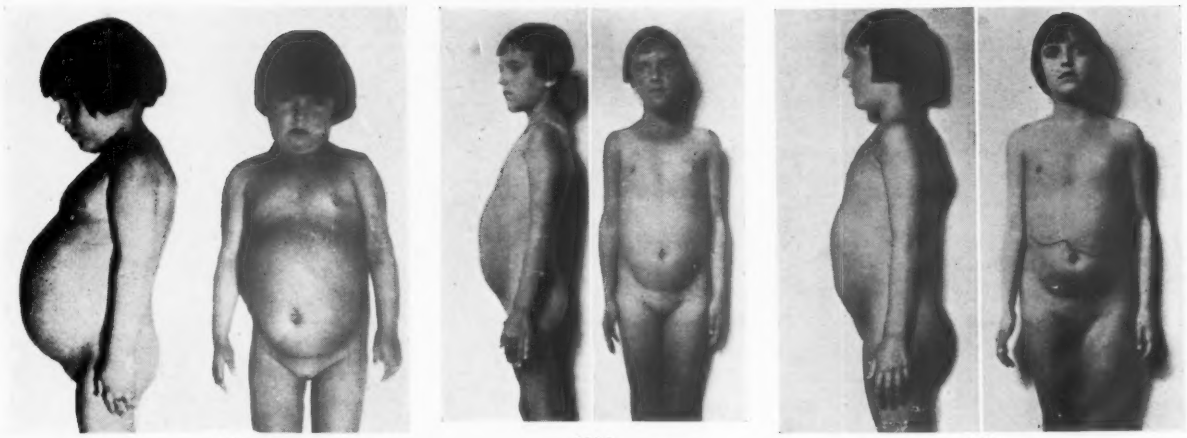
The urine in the fasting condition contains only a trace of acetone or none and she never has glycosuria. In Table 2 the results of laboratory tests performed since 1938 are summarized.

In 1938, at the age of 11 years, the liver was moderately enlarged and the spleen was just palpable. The urine in the fasting condition still had a positive reaction to acetone and urobilin. The blood cholesterol content was slightly increased. The fasting blood sugar content was normal and the glucose tolerance test showed a biphasic curve. The albumin-globulin ratio was normal, with the exception of a slightly increased globulin content. The abnormal biochemical findings were fewer in 1938 and to a lesser degree than when the patient was seen for the first time at the age of 5 years. In 1943, she contracted infectious hepatitis: the liver became greatly enlarged, the spleen remained just palpable. The urine showed a negative acetone reaction and a strongly positive urobilin reaction. The fasting blood sugar content was very low and after ingestion of glucose it showed a marked increase with a return to the very low original value within two hours. The serum cholesterol content was very low and the albumin-globulin ratio showed an extremely high globulin content.

In 1948 the patient was 21 years of age. The hepatomegaly had disappeared, the spleen remained just palpable. The urine on fasting did not contain acetone and only traces of urobilin. The serum cholesterol content and the serum proteins were approximately normal. Some liver function tests were almost normal. The fasting blood sugar content was normal again, but after adrenalin injection there was practically no response, and the reaction for acetone in the urine was slightly positive on only one occasion after adrenalin injection.

In July, 1951, when she was 24 years old, we were able to examine our patient once more. The urine contained a trace of urobilin, and, after adrenalin injection, only once a trace of acetone. The fasting blood sugar content was normal now, and after adrenalin injection it did not rise during the first half hour, and after that only slightly. The simultaneous determinations of lactic acid showed some slight variations. The serum proteins were normal. The blood glycogen content was increased. The glycogen content of the leucocytes, which, according to Wagner (1947), should also be increased considerably in glycogen liver disease was 4 γ per million leucocytes, thus at the upper limit of normal mean values.

It may be concluded that both patients still have some metabolic disorders similar to those found in the beginning of their disease. Changes in the blood sugar and lactic acid content after adrenalin injection are still absent though the fasting blood sugar has reached normal values. The fact that



1932 1936 1938

FIGS. 3 and 3A.—Photographs showing decreasing size of the liver in our second patient.

both patients after adrenalin injection do not show a normal glycaemic reaction at present points to abnormal mobilization of liver glycogen into glucose. On the other hand, it appears that the quantity of glucose available for utilization is sufficient, probably by the increased fasting blood sugar content. The signs of an increased combustion of fat (ketonuria) in the fasting condition and after adrenalin injection are now absent or much smaller than formerly. The raised serum cholesterol has disappeared. It is probable that the mobilization of muscle-glycogen after adrenalin injection is still disturbed, as may be seen from the fact that the lactic acid content of the blood remains unchanged as well.

1948 1951

FIG. 3A.

From these observations in two cases of glycogen liver disease, which we were able to follow up for so many years, it appears that the prognosis is not necessarily unfavourable. In not one case of glycogen liver disease have we seen the transition into diabetes mellitus observed in the case of Parnas and Wagner (1922).

Aetiology

In the course of years the aetiology as well as the therapy of glycogen disease have frequently been discussed. To explain the aetiology of glycogen liver disease the problems concerned with glycogen metabolism in the liver and other organs must first be considered. Formerly the breaking down of glycogen in the liver was ascribed solely to the presence of an amylase. It was astonishing to find glycogen storage in the liver (and other organs) in glycogen disease, though glycogenase could be demonstrated. By the investigations of Cori and Cori (1931), de Duve (1945) and others it has become clear that in glycogen disease the presence of amylase in the liver has little or no significance. In the breaking down of glycogen in the liver are processes of phosphorylization partly analogous to those which occur in the muscles. Until recently it was impossible to detect a disturbance in one of these processes in glycogen disease, though the hypothesis that such a disturbance would be present had been expressed several times. One of the difficulties is that the material has to be examined immediately after a biopsy or after death. However, quite recently Mrs. Cori made a very important discovery which was reported to me by Prof. A. F. Hartmann, of St. Louis. In a typical case of glycogen disease in a baby she examined the composition of the liver with regard to its metabolism. She was able to demonstrate that the glycogen was quite normal. The glycogen in glycogen storage disease is identical in chemical structure with normal glycogen. Furthermore the concentration of all kinds of enzymes involved in the phosphorylization processes was normal, but the specific phosphatase of glucose—6—phosphate was either entirely lacking, or was present in only a very small quantity. This could

TABLE 2

HEPATOMEGALIA GLYCOGENICA IN CASE 2

	1938	1943*	1948	1951		
Height (cm.)	125		167	167		
Weight (kg.)	26		63·3	65		
Proteins (%)	in plasma	in plasma	in serum	in serum		
Total	7·62	9·03	6·06	5·9		
Albumin	4·72	3·5	3·99	3·73		
Globulin	2·55	5·17	2·07	2·17		
Fibrinogen	0·35	0·36	—	—		
Cephalin flocculation-test			+			
Takata-Ara test	—	+	+			
Glycogen in blood (mg.%)				21·2		
Glycogen per million of leucocytes (γ)				4		
				After 0·5 ml. Adrenalin 1/1000		
Blood sugar curve	After 30 g. Glucose (mg.%)	After 50 g. Glucose (mg.%)	After 0·75 ml. Adrenalin 1/1000 (mg.%)		Blood Sugar (mg.%)	Lactic Acid (mg.%)
Fasting	86	46	84		92	18
after 30 min.	161	140	After 10 min. 82	After 15 min.	84	16·9
„ 60 min.	100	184	„ 20 min. 88	„ 30 min.	89	23·4
„ 90 min.	141	170	„ 30 min. 86	„ 60 min.	100	16·7
„ 120 min.	123	97	„ 60 min. 92	„ 90 min.	100	15·8
„ 150 min.	119	40	„ 90 min. 95			
			„ 120 min. 91			
			„ 150 min. 83			
Urine						
Acetone (fasting)			—	Trace +		
After adrenalin injection						
Acetone	+	—	+	+		
Diacetic acid	—	—	—	—		
Urobilin	++	++	Slightly +	Trace		
Sugar	—	—	—	—		
Hepatomegaly	+	++	Absent	Absent		
Splenomegaly	+	+	Slightly palpable	Slightly palpable		

* In 1943 the patient had infectious hepatitis.

be the explanation of the disturbance in glycogenolysis.

Sufficient arguments exist in favour of the conception that in glycogen disease hormonal factors are also of great importance. Recent researches have stressed the possible significance of A.C.T.H. in glycogen disease. On this subject and on the possible part played by the pituitary gland in general in glycogen disease, the case of glycogen liver disease in a girl 3 years old is interesting. In the urine of this child, Dr. Dingemanse and Dr. Huis in 't Veld found a very low value for the 17-ketosteroid excretion (0·9 and 1·2 mg./24 hours). An A.C.T.H. preparation, 'cortrophin', of which the injection of 1 mg. in a patient with a strong eosinophilia had caused a marked diminution in eosinophils, was given in small amounts for two days (0·5 mg. four times a day) and caused a significant decrease in the glycogen of the leucocytes. Before the injections the glycogen content was increased (7·3, 6·6, and 5·9 γ per million leucocytes); after the injections it decreased to 3·2 and 2 γ. According to Wagner the normal maximal value is 4·43 γ per million leucocytes. It cannot be ascertained whether under the influence of A.C.T.H. more glycogen

has been stabilized as glycogen or that more glycogen has been used by the metabolic process.

Treatment

At present no established therapy in glycogen disease exists. Administration of amylase or of hormone preparations has not given any result. The combination of hypoglycaemia and acetonuria has suggested the prescription of a diet rich in carbohydrates and poor in fat. The preference for carbohydrates (bread, potatoes) of the patients sometimes gives rise to such symptoms as nausea and fatigue. The oral ingestion of choline, as prescribed to one of our patients after the publications of Best, may have some influence on the ketosis, especially when there is reason to believe that the liver contains a great deal of fat as well as glycogen. Bridge and Holt (1945) have recommended that these patients should take an extra quantity of proteins in the evening in order to eliminate the detrimental consequences of an increased transformation of proteins into glycogen. Lowrey and Wilson (1949) recently observed a case of glycogen liver disease in a boy of 2 years, in whom the symptoms of hypoglycaemia could be favourably influenced by the administration of large quantities of proteins and small quantities of carbohydrates. Matheson (1949), like other investigators, observed in one case the quick disappearance of the ketonuria and reduction of the distended abdomen after giving bile salts. These therapeutic measures have no fundamental effect on the disease.

Summary

A short survey is given of the early history of glycogen disease. The diagnosis and differential diagnosis of the two principal types of the disease are discussed. The clinical course and the development of typical metabolic findings up to date are communicated of the two cases of the hepatomegalic type of the disease described by the author for the first time in 1928 and 1932 respectively.

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POLIOMYELITIS IN INFANTS UNDER THE AGE OF 6 MONTHS

BY

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Reported cases of poliomyelitis in infants under the age of 6 months are rare, especially in the British literature, none having been recorded since 1918 (Gunewardene, 1918). Aycock and Kramer (1930), on the basis of virus neutralization tests, suggested that the infrequency of cases under 1 year of age was due to the passive transmission of immune bodies through the placenta, and although only one group of workers (Ward, Horstmann and Melnick, 1946) have isolated the virus from the blood, one case of possible intra-uterine infection was reported by Baskin, Soule and Mills (1950). This case in a 5-day-old infant is the youngest in the literature.

Mouton, Smillie and Bower in 1950 could find only 10 previously recorded cases of poliomyelitis under the age of 6 months and reported 10 more. Since then Baskin, Soule and Mills (1950) have reported two cases occurring in the neonatal period.

During the 1950 epidemic of poliomyelitis the disease occurred in 10 patients aged under 6 months out of a total of 243 cases of poliomyelitis admitted to the Northern Ireland Fever Hospital. The age incidence of the disease during this epidemic was more nearly that of the textbook description than in 1947 when none of 78 cases admitted was under 6 months of age. The age incidences in the two epidemics are compared in Table 1.

Case Records

These are summarized in Table 2.

Case 1: P. McD. A girl aged 2 months was admitted on the fourth day of her illness with a history of general apathy and refusal to feed. She had not been vaccinated nor had she been immunized against diphtheria or pertussis.

On examination she was slightly cyanosed and completely disinterested in her surroundings. There were no meningeal signs and the fontanelle was normal but there was a flaccid paralysis of both arms and the neck muscles. Limited weak movement of the legs occurred in response to painful stimuli, while the knee and ankle jerks were depressed. Breathing was entirely diaphragmatic and a few râles were audible at the base of the left lung. The cerebrospinal fluid (C.S.F.), which was under a slightly increased pressure, contained 80 mg. of protein and 52·5 mg. of sugar per 100 ml., while the cells numbered 114 per c.mm.

The child was nursed in an oxygen tent and the next day her colour had improved. Some movement of the hands was observed, but the arms and neck muscles remained paralysed and the left leg had become completely flaccid. Two days after admission, despite apparent improvement in the function of the intercostal muscles, the child died quite suddenly. A post-mortem examination was not performed.

Case 2: P. McV. A boy of 5 months was admitted on the seventh day of his illness. He had a history of vomiting and diarrhoea on the day of onset, followed three days later by head rolling and on the fourth day by

TABLE 1

COMPARISON OF AGE INCIDENCES IN TWO OUTBREAKS OF POLIOMYELITIS IN NORTHERN IRELAND

Age (in years)	0–½	½–1	1–3	3–6	6–9	9–12	12–20	Over 20	Total
1947 ..	0	2	11	15	10	7	13	20	78
1950 ..	10	16	74	42	34	11	28	28	243

paralysis of both legs. He had not been vaccinated nor had he been immunized against diphtheria or pertussis.

On examination he was markedly irritable but showed no meningeal signs. Both legs and the right arm were paralysed, with loss of the tendon reflexes. There was limited weak movement of the left arm and hand. No abnormality of cranial nerve or respiratory muscle function was detected. The ear drums were healthy. The C.S.F. was clear and contained 80 mg. of protein and 50 mg. of sugar per 100 ml. and 31 cells per c.mm.

No spread of the paralysis occurred and 10 days after admission feeble movements of the toes were observed while strength returned quite rapidly to the left arm. On transfer to an orthopaedic hospital three months later the legs had shown no further improvement.

Case 3: J.H. A boy of 5 months was admitted on the twelfth day of his illness. He had a history of feverishness and irritability for five days followed by weakness of both legs. Vaccination had not been performed nor had he been immunized against diphtheria or pertussis.

On examination no meningeal signs were elicited. There was a complete flaccid paralysis of the right leg and well marked spasm of the gastrocnemius and quadriceps muscles of the left leg. The arms and cranial nerves were normal. The C.S.F. contained 50 mg. of protein and 60 mg. of sugar per 100 ml. and 56 cells per c.mm.

The left leg subsequently became flaccid and on discharge, four months later, no improvement had occurred apart from the return of a weak contraction in the right quadriceps.

Case 4: P.G. A girl of 3 months was admitted on the seventh day of her illness with a history of irritability for two days followed by weakness of the arms and neck muscles. The child had been successfully vaccinated in the left arm six weeks before the onset of the illness but had not been immunized against diphtheria or pertussis.

On examination there was a flaccid paralysis of both legs and the right arm. The left hand grip was strong but no movements could be elicited at the left elbow or shoulder joints. Painful stimuli caused weak flexion and extension of the toes but the tendon reflexes in the legs could not be elicited. The C.S.F. contained some traumatic blood. The supernatant fluid was clear and contained 70 mg. of protein and 60 mg. of sugar per 100 ml.

Movements returned slowly to all limbs, first to the right hand, then to the arms and finally to the legs. On discharge, three months later, the only residuum was weakness of the left shoulder.

Case 5: J.D. A boy of 5 months was admitted on the fifth day of his illness. He had been irritable, out of sorts and off his feeds, and was observed to have paralysis of the left arm. He had not been vaccinated nor had he been immunized against diphtheria or pertussis.

On examination the child was pale and irritable. There was a flaccid paralysis of the neck muscles, both arms and forearms. Finger movements were present in both hands and although the child was unable to sit up the legs appeared to be strong. The C.S.F. contained 40 mg. of protein and 52 mg. of sugar per 100 ml. and the cell count was 214 per c.mm.

Gradually all the paralysed muscles recovered and on discharge two months later the child was apparently normal.

Case 6: C.P. A girl of 4 months was admitted on the eighth day of her illness with a history of malaise, irritability and a weak cry. On the day of admission the left arm was noticed to be weak. She had not been vaccinated nor had she been immunized against diphtheria or pertussis.

On examination the child was irritable but meningeal signs were absent. Paralysis was limited to the left arm and shoulder girdle. A weak contraction was palpable in the left biceps. The C.S.F. contained 50 mg. of protein and 40 mg. of sugar per 100 ml. and 36 cells per c.mm.

The condition failed to respond to treatment, and on discharge two months later marked wasting of the left shoulder girdle had occurred.

Case 7: D.McF. A boy of 5 weeks was the heavier of premature twins born in a maternity hospital. He was discharged before his twin at the age of 3 weeks. Ten days later he developed fever, vomiting and constipation. On the fourth day of his illness the child was admitted to another hospital where he was treated with intramuscular penicillin and streptomycin. After 48 hours meningeal signs became evident and a lumbar puncture was performed. The C.S.F. contained 90 mg. of protein and 48 mg. of sugar per 100 ml., and 190 cells per c.mm. Following lumbar puncture he was transferred to the Northern Ireland Fever Hospital on the sixth day of his illness. He had not been vaccinated nor had he been immunized against diphtheria or pertussis.

On examination the child looked exhausted and had a weak persistent cry. No movement of the legs, right arm or intercostal muscles could be detected.

Although movements of the toes and left leg improved slightly the right leg wasted rapidly and contractures developed in both feet. The chest became grossly deformed as a result of the purely diaphragmatic breathing and after six months in hospital the child died of bronchopneumonia. No necropsy was carried out.

Case 8: M.W. A girl of 5 months was admitted on the seventh day of her illness having been feverish and irritable with vomiting and constipation. The child was breast-fed and had been successfully vaccinated three months previously but had not been immunized against diphtheria or pertussis.

On examination she was very irritable and had a mild thrush stomatitis. There was a flaccid paralysis of both legs and considerable weakness of the left arm, the tendon reflexes being absent. The C.S.F. contained 60 mg. of protein and 40 cells per c.mm., but the sugar content was not estimated.

After admission the paralysis spread to involve the abdominal muscles and the right arm, the fingers and

wrists, however, escaping. At the time of discharge three months later the abdominal and both deltoid muscles were still paralysed and apart from weak contraction of the left quadriceps no improvement had occurred in the legs.

Case 9: R.C. A boy of 5 weeks was admitted on the fifth day of his illness with a history of pyrexia and failure to feed. He had had penicillin injections three-hourly for 48 hours before admission but had not been vaccinated nor had he been immunized against diphtheria or pertussis.

On examination he had a flaccid paralysis of both legs and the right arm. The left arm was weak but the tendon reflexes were still present. The cranial nerves and muscles of respiration did not appear to be affected. The C.S.F. contained some traumatic blood, 200 mg. of protein and 48 mg. of sugar per 100 ml.

The paralysis did not spread but six months later little improvement had occurred. There was a weak flexion movement in both hips but otherwise the legs were flaccid and a complete paralysis of the right shoulder girdle persisted.

Case 10: M.McC. A boy of 16 days was admitted on the second day of his illness with a history of anorexia, the sudden onset of harsh breathing and twitching of the left side of the face. The birth at home had been uneventful and the child developed normally before the beginning of the illness.

On examination no meningeal signs were observed. Breathing was entirely diaphragmatic and the left side of the forehead twitched at long intervals. Muscle spasm was palpable in both legs but the arms were flaccid. The C.S.F. contained 100 mg. of protein per 100 ml. and 130 cells per c.mm.

The child was nursed in an oxygen tent and fed well from a pipette. His condition changed little during the next few days but later he was able to be nursed out of the tent. On the ninth day of illness, however, a convulsion occurred. This was controlled by general anaesthesia but the child died following two further convulsions three hours later.

A post-mortem examination was performed 14 hours after death by Dr. A. R. Crawford and the principal findings have been abstracted from her report:—

Macroscopically the only abnormalities detected were a few petechial haemorrhages beneath the endocardium of the left ventricle and a firm, deeply haemorrhagic area in the anterior papillary muscle of the left ventricle.

A microscopical examination gave the following picture:

Spinal Cord. This showed pathological changes typical of anterior poliomyelitis. These were relatively mild in the thoracic cord but severe in both the lumbar and cervical enlargements.

Medulla. There were bilateral lesions in the medulla mostly in the area dorsal to the inferior olivary nucleus. At another level more recent lesions consisted of large areas of necrosis with some haemorrhage into them and lymphocytes cuffing the neighbouring vessels.

Pons. Near the dorsal aspect the pons showed a large area of recent necrosis containing numerous small haemorrhages. In other parts of the sections there were small foci of cellular infiltration, lymphocytic cuffing of some vessels and chromatolysis of nerve cells.

Basal Ganglia. These also showed areas of recent necrosis and haemorrhage, the largest being about 5 mm. in diameter.

Motor and Pre-motor Cortex. Sections showed only congestion and chromatolysis of some nerve cells.

Cerebellum. No pathological changes were seen.

Heart. Sections of the left auricle and left ventricle showed evidence of widespread myocardial damage. In the ventricle there were numerous areas of focal necrosis infiltrated by a few lymphocytes and large mononuclear cells. The tip of the papillary muscle was completely necrotic and full of recently extravasated blood cells.

The endocardium and pericardium appeared normal.

Lungs. Sections of the lower lobes showed small areas of collapse. Some alveoli contained red blood cells and there were also groups of phagocytic cells with foamy cytoplasm. There was infiltration of the peribronchial interstitial tissue by lymphocytes and large mononuclear cells.

Discussion

Symptoms and Signs. The history of the onset of the illness obtained in these 10 cases is probably incomplete as the information was usually obtained several days after the children were admitted to hospital when the parents came to visit them. Nevertheless they are worthy of comment if only to stress their indefinite nature. Irritability and refusal to feed were the most common presenting symptoms. Vomiting, which occurred in three cases, constipation in two, and diarrhoea in one, have not previously been recorded as symptoms of poliomyelitis in this age group. Mouton, Smillie and Bower (1950), reporting 10 cases, commented that gastro-intestinal upsets were conspicuous by their absence.

Paralysis was observed by the parents in only four cases before admission.

Meningeal signs, so common in adult poliomyelitis, are seldom observed in the infant. In only one of the 10 cases in this series were they present on admission to hospital, but, as few of the cases were admitted early in the course of the disease, they may well have occurred during the initial stages.

Cases of poliomyelitis occurring in the neonatal period and associated with infection in the mother or immediate family have been recorded (Biermann and Piszczek, 1944; Baskin, Soule and Mills, 1950). In all these cases the presenting sign was pyrexia and other physical signs, apart from paralysis, were uncommon.

In this age group convulsions, at any stage of poliomyelitis, have not previously been reported

TABLE 2
SUMMARY OF CASE RECORDS

Case Number	Age	Sex	Symptoms	C.S.F.	Paralysis	Result
1	2 mths.	F	Anorexia Apathy	P 80 C 114 S 52·5	Neck Intercostals Both arms Left leg	Died 6th day
2	5 mths.	M	Irritable Vomiting	P 80 C 31 S 50	Arms Trunk Both legs	Legs flaccid. Trunk and right arm improved
3	5 mths.	M	Irritable	P 50 C 56 S 60	Legs	Right leg improved. Left leg flaccid
4	3½ mths.	F	Irritable	P 70 C Blood S 60	Neck Left arm and shoulder Both legs	Legs probably normal. Arm and shoulder weak
5	5 mths.	M	Irritable	P 40 C 214 S 52·5	Neck Both arms	Complete recovery
6	4 mths.	F	Irritable	P 50 C 36 S 40	Left arm	No change
7	5 weeks.	M	Vomiting Pyrexia	P 90 C 190 S 48	Intercostals Both arms Partial legs	Died. Bronchopneumonia in convalescence
8	5 mths.	F	Irritable Vomiting Pyrexia	P 60 C 40	Neck All limbs	Arms improved. Legs little changed
9	5 weeks	M	Anorexia Pyrexia	P 200 C Blood S 48	Both legs Right arm	Legs flaccid Arm improved
10	16 days	M	Off feeds	P 100 C 130 S 53	Both arms Intercostals	Died 9th day

P=Protein C=Cell count S=Sugar

and their occurrence, in Case 10, makes this case unique.

Association of Paralysis and Injections. None of the 10 cases reported had been immunized against diphtheria or pertussis, but in three cases there was a possible relationship between the site of paralysis and a previous recent injection.

Cases 7 and 9 had penicillin injections during the initial pyrexial period of their illness and subsequently developed paralysis of the thighs, the site of the injections. Case 4, N.P., had been vaccinated six weeks before the onset of the illness and developed paralysis of the left arm and shoulder. Three cases of poliomyelitis following vaccination have been reported (Jermulowicz, 1930; Banerjea, 1935). In the two cases described by Jermulowicz permanent flaccid paralysis developed in the left arm and shoulder girdle 11 and 14 days respectively after vaccination. There was no sensory loss. No other cases of poliomyelitis were seen in the district for three months after these cases occurred. Banerjea's case, a child of 1 year 10 months, developed a flaccid quadriplegia, without sensory loss, 35 days after vaccination which had been performed with two insertions in each arm. She subsequently recovered function in the right arm. No other children in the family developed any

TABLE 3

SEASONAL INCIDENCE OF INFANTILE CASES AND OF CASES ADMITTED DURING THE SAME PERIOD

	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Series				3	2	2	1	1	1				
All ages ..	1	1	4	9	17	43	59	52	38	12	7		243

illness although two of them were vaccinated at the same time.

Seasonal Incidence. Table 3 shows the seasonal incidence of the infantile cases and that of cases of all ages admitted to hospital during the same period.

Treatment. In the initial stages of the illness all cases were sedated, usually with bromide, and those able to be moved had, at least once a day, a hot bath with passive movements, within the limits of pain. After two weeks a comprehensive muscle survey was made on each patient by an orthopaedic surgeon. Physiotherapists, working under the direction of the surgeon, then initiated active and passive movements using heat and splints as indicated.

Results. Only one case, No. 5, can be regarded as having completely recovered. The others were disappointing, for, despite movements, splints and massage, muscle wasting developed rapidly and contractures often followed because of the difficulty in maintaining good position, splints being badly tolerated at this age. Three of the patients died.

Summary

Ten cases of poliomyelitis in infants under the age of 6 months are described in detail. These occurred during the 1950 epidemic in Northern Ireland.

The post-mortem findings in one case which had convulsions are summarized.

The symptoms and signs are discussed.

I wish to express my thanks to Dr. F. F. Kane for permission to publish these cases, to Dr. A. R. Crawford for the post-mortem report, and to Dr. G. W. F. Tinsdale for the C.S.F. reports.

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HERPES ZOSTER NEONATORUM

BY

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In spite of the widespread occurrence of herpes zoster few cases have been reported in the newborn. As long ago as 1889 Lomer reported its occurrence in an infant aged 4 days and mentioned that a similar case had been reported by Bohn 20 years earlier. Further cases have been reported by Gaehde (1897), Kalb (1909), Bonar and Pearsall (1932), Tausch (1932), Katayama (1938), Freud, Rook and Gurian (1942) and Counter and Korn (1950).

The case described by Kalb (1909) is interesting because of multiple symmetrical scar formation in the distribution of the first and second divisions of the trigeminal nerves which was considered to be due to a possible intra-uterine infection with zoster.

In Katayama's series of 487 cases only one occurred in the newborn, and in a series of 1,406 cases of herpes zoster reviewed by Lang (1938) there were no cases in children under the age of 4 years. Comby (1922) reported 84 cases which had occurred in children under the age of 15, but the youngest child was 8 months old.

In view of the rarity of herpes zoster in the newborn it was thought worth recording the following case which has the added interesting feature that it occurred in a twin, the other twin being unaffected.

Case Report

Twin infants were born on April 21, 1951. The first twin, the subject of this report, presented by the breech with extended legs. Delivery was difficult and was effected by fundal pressure, episiotomy and traction to the right groin during five contractions, forceps being applied to the after-coming head. The second twin was delivered as a vertex and was normal. No resuscitation was required and both infants were well.

On the fourth day after delivery a herpetiform eruption of a single line of vesicles the size of a pin-head on an erythematous base appeared on the right thigh and by the fifth day extended from the middle of the right buttock to the middle third of the calf, extending along the course of the sciatic nerve to the lower margin of the popliteal fossa where it divided, and scattered lesions were present on the postero-lateral and postero-medial aspects of the calf. There were no other lesions elsewhere on the body. By the ninth day the original lesions had dried but a few new vesicles appeared on the lower third of the calf. When seen on the twenty-second day only superficial scarring remained. The infant showed no evidence of constitutional upset during the course of the disease and was apparently not in pain.

The course of the pregnancy had been uneventful in the main but the mother stated that she suffered from herpes zoster just before or at the beginning of the pregnancy, though she could not be definite about the exact date. She had had measles and chickenpox during childhood. There was a strong family history of tuberculous infection but the mother herself showed no signs of active infection.

Virus Investigations. Fluid from fresh vesicles taken on the fifth day of life was treated with penicillin and streptomycin and inoculated intracerebrally into adult and sucking mice and onto the chorio-allantois of three 12-day-old chick embryos. The mice remained well and no lesions appeared on the chorio-allantoic membranes. Passage of these membranes to a second batch of eggs produced no herpetic or vaccinial lesions.

A stained smear of vesicle fluid contained bodies of a size similar to elementary bodies of the pox group of viruses but no definite opinion could be given as to their identity.

A further interesting feature is that the obstetrician who delivered the twins developed herpes zoster 14 days later (10 days after the development of the eruption on the infant), and the bacteriologist who took scrapings from the lesion for culture also developed herpes zoster, 15 days after contact with the infant.

Discussion

Trauma is known to precipitate the rash, and this is supported by the case of Bonar and Pearsall (1932) in which traction on the head at delivery, with probable trauma to the brachial plexus, was

SEROLOGICAL TESTS WITH HERPES SIMPLEX VIRUS

Serum	Date	C.F.T. with C.A.M. Antigen				Neutralization in Virus-serum Mixtures on Chorio-allantois (%)
					*	
Mother	26.4.51	1/12	++++	1/24	++	99·7
Infected twin	26.4.51	1/12	++++	1/24	—	99·6
A.W. (infected twin)	11.5.51	1/3	++++	1/6	—	98·8
P.W. (normal twin)	11.5.51	1/3	++++	1/6	±	97·9

* Degree of fixation at serum dilutions stated.

followed by the eruption of herpes zoster on the arm. The cause of the eruption on the course of the right sciatic nerve in the one twin while the other was unaffected may well be explained by the trauma to the right leg from traction on the right groin while the legs were extended during delivery.

In Katayama's (1938) series the sacral distribution of herpes zoster was the rarest, whereas in three reported cases occurring in the newborn, and in the present case, the sacral nerves were involved. Thus it has occurred in four of 10 cases in the newborn as compared with 24 of 487 at other ages collected by Katayama.

The mode of infection in this case is not clear. It is known that the mother had herpes zoster just before, or in the early weeks of, pregnancy, but to her knowledge she had not been in contact with either herpes zoster or chickenpox since then. This suggests that if the infection occurred during the early weeks of the pregnancy the developing foetus became infected before maternal antibodies could be formed, in which case the virus survived in the infant until after birth.

In one of the reported cases serious ill effects were noted, convulsions and death occurring soon after the eruption (Gaehde, 1897). In all other cases, including the present one, the rash appears to have produced little if any constitutional or local upset.

The infant described by Counter and Korn (1950) was subsequently found to be blind but this may not have been related to the herpes zoster.

Although the diagnosis of herpes zoster was not in doubt clinically, it was thought of interest to exclude the possibility of herpes simplex infection. The falling titre in the complement fixation test on the affected infant's serum was against a diagnosis of herpes simplex. The negative culture was also a factor in favour of a diagnosis of zoster and against that of herpes simplex in view of the fact that the herpes virus can be readily isolated in the acute phase of an illness.

Summary

The literature of herpes zoster in the newborn is reviewed.

A case occurring in one infant of a twin pregnancy is described.

Trauma is a possible factor in precipitating the rash in this instance.

It is suggested that possibly the foetus may have been infected in the early weeks of pregnancy.

My thanks are due to Professor Wilfrid Gaisford for helpful advice and criticism; to Dr. G. M. Komrower for permission to publish the case under his care; to Dr. A. Holzel for translating the literature; to Dr. J. O'H. Tobin for the virus investigations.

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BLOOD FORMATION IN INFANCY

PART I. THE NORMAL BONE MARROW

BY

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A complete account of the changes in the blood picture in infancy requires a knowledge of the rates of formation and destruction of blood. Since the latter is not easily measured, our approach has been to use the activity of bone marrow as a measure of blood formation, and then to deduce whether changes in blood formation alone are sufficient to account for observed changes in the blood picture. Part I of the study, therefore, consists of an account of the marrow picture during the first three months of life. Part II concerns erythropoiesis, and the marrow findings are then considered together with the blood picture.

Material and Methods

The data to be discussed are derived from a total of 102 specimens of marrow from 25 infants aged from a few minutes to three months. A sample of venous blood was taken at the same time as the marrow.

The infants were born in the Cambridge Maternity Hospital; the majority were chosen because their mothers had already borne a normal infant at the hospital and had volunteered to take part in the investigation; three subjects were mongols, but as their weight gains proved normal during the period under review, they were included in the series. Labour and delivery were normal, minimal nitrous oxide and air anaesthesia being given to the mothers. Birth weights exceeded 6 lb. The cord was clamped as soon as conveniently possible, but usually some 10 to 15 seconds elapsed before this was done. Infants developing more than trivial infections were excluded. Sixteen of the 25 infants were completely breast fed. Weight gains were satisfactory and the infants generally were healthy and well cared for.

Samples of marrow and venous blood were taken when possible at the following ages: birth, first day, 3-5 days, 8-10 days, 1 month and either 2 or 3 months. Not every infant completed the full two or three months, hence there are more data for the first month than for later, but 14 infants were followed for the full two to three months.

Marrow Samples. These were obtained by tibial puncture using the technique and special needles described by one of us (J.D.R.) (Gimson, 1944). The procedure takes no longer than a venipuncture and no anaesthetic was used. The method has been used on about 250 occasions in young infants, with very rare failure to obtain a good sample of marrow. After trying other sites, sternum, ilium, vertebra and femur, we have found tibial puncture the most reliable method for young infants: 0·25 ml. of marrow was aspirated, smears made, and the remainder mixed with Wintrobe's oxalate mixture (Wintrobe, 1946). From the oxalated marrow total nucleated cells were counted in a white cell chamber. A differential cell count of 200 cells was performed on the marrow films. Smear cells were counted separately (see below). The nomenclature given by Whitby and Britton (1950) has been used throughout.

Venous Blood. This was obtained from the internal or external jugular vein and mixed with Wintrobe's oxalate mixture. Cord blood was obtained by umbilical vein puncture after clamping the cord. Haemoglobin was determined as oxyhaemoglobin in a photoelectric colorimeter. The blood dilution was 1 in 200, using 0·04% ammonia as diluent. The colorimeter was checked weekly against the Medical Research Council type grey wedge standard photometer (Duffie, 1945). A further check of both instruments was made monthly with iron determinations on several blood samples. Erythrocyte and leucocyte counts were made by conventional methods, counting 0·005 c.mm. of blood for the red cells, and 0·04 c.mm. of blood for the leucocytes. Differential leucocyte counts were performed on films made with an automatic slide-making machine (Marks, Bailey and Gunz, 1950), counting 200 cells by the battlement technique (MacGregor, Richards and Loh, 1940). Packed cell volume was estimated in a Wintrobe haematocrit tube, spun for 30 minutes at 3,000 r.p.m. Reticulocytes were counted by a modification of the Della Vida technique after counterstaining with Leishman, a preliminary investigation having shown that this gave reproducible results: one thousand red cells were enumerated, a number insufficient to give results of great accuracy, but sufficient to show the large

alterations in reticulocyte level which occur in infancy.

Total Circulating Haemoglobin and Red Cells. In view of the rapidity of body growth in infancy, concentrations of blood cells may give a misleading idea of alterations in their absolute number, and it has proved convenient to estimate the total number of the various types of cells in the circulation from the product of their concentration and the blood volume. These have been derived as follows. The observed concentrations of haemoglobin and red cells in venous blood have been multiplied by the factor 0·87 to allow for venous blood having a higher concentration of red cells than has the circulating blood as a whole (Mollison, Veall and Cutbush, 1950). No such correction has been applied to the white cells since, in the absence of information on this point, we have assumed that their concentration in venous blood is representative of the blood as a whole. Blood volume has been calculated from the data recently published by Mollison *et al.* (1950) and Mollison (1951) where blood volume is shown as a function of body weight and 'venous haematocrit'. Mollison derives 'venous haematocrit' from the observed packed red cell volume (P.C.V.) by the formula (P.C.V.—2·0)× 0·95. The factor 0·95 is a correction to allow for plasma trapped in the red cell layer. The 2 units subtracted from P.C.V. in the formula allows for the difficulty in reading the top of the red cell layer precisely when working with blood from young infants, owing to the red and white cell layers sometimes merging indefinitely. We have observed the same phenomenon, but only in blood of infants in the first day of life, and have then attempted to allow for it by taking as the top of the red cell layer a point half way up the indefinite zone. For this reason we have preferred to take 'venous haematocrit' as simply P.C.V. ×0·95. The blood volume obtained by Mollison and his colleagues were derived data from infants less than 24 hours old, but they give cogent reasons for believing that they apply equally to adults, hence it seems reasonable to apply them to older infants, and this we have done, considering that no more accurate figures are available. However, inspection of the curve connecting blood volume and venous haematocrit (Mollison, 1951) shows that blood volume begins to increase to an important degree with increasing haematocrit only when the latter reaches high levels. It happens that our main conclusions have not depended upon observations involving these high haematocrits, and hence, had we chosen to compute blood volumes as a fixed proportion of body weight, this would have made no significant difference to these conclusions.

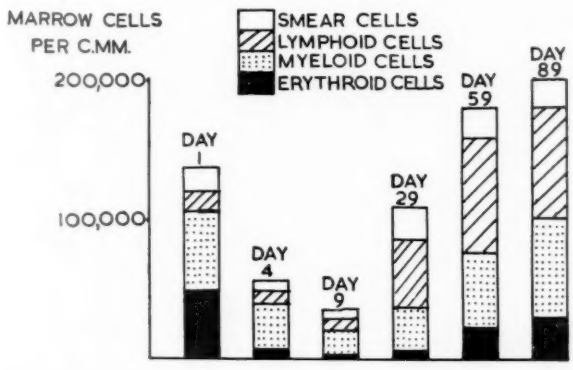

FIG. 1.—The cellular pattern of the bone marrow from birth to 3 months. (The small number of monocytes is not shown.)

Results and Discussion

Since the data on marrow refer to tibial marrow, conclusions drawn from this would only be valid if the red marrow throughout the body could be considered homogeneous. This uniformity has been found in adults by Stasney and Higgins (1939) who examined marrow from the sternum ribs, vertebrae and femora of 14 subjects after accidental death by Rubinstein, (1948), who compared 216 marrows from iliac crest and sternum, and by Leitner (1949) who punctured sternum, ribs and vertebrae in 10 cases. In children Lamy, Sée, Chiche and Montefiore (1939) obtained similar results on the sternal and tibial marrow up to 8 years of age but give no details. Traina and Velasco (1949) studied the marrow of sternum, tibia, femur and vertebrae in 12 infants who presented a normal peripheral blood picture and could find no significant differences between samples from different puncture sites, while Lato (1947) could find no difference between marrow from sternum, tibia and iliac crest in either healthy or diseased children.

To confirm these findings in the neonatal period, we have performed a number of multiple marrow examinations.

(1) Histological sections were examined from several bones of each of 10 infants who had died soon after birth or had been stillborn. Marrow from the different sites showed no significant differences in total cellularity or in relative numbers of the different marrow cells.

(2) In seven infants dying shortly after birth, three from obstetric causes and four from haemolytic disease, marrow punctures were made from three or more sites—sternum, femur, iliac crest or tibia. The different sites showed a uniformity both of total cellularity and differential count.

(3) Multiple marrow punctures were performed on four live infants. Marrow from different sites showed no major differences of total cellularity or differential count (Table 1).

Total Nucleated Cell Count. In 94 samples a total nucleated cell count was performed. In the remaining eight insufficient marrow was obtained for a count and the cellularity was estimated from the stained smear, for with experience it was found that the total nucleated cells could be estimated

TABLE 1

CELL COUNTS OF MARROW SAMPLES FROM TWO OR MORE SITES*

	Case 1		Case 2		Case 3		Case 4		
Age	4 days		11 days		28 days		5 days		
Site	Left Tibia	Right Tibia	Sternum	Right Tibia	Sternum	Left Tibia	Sternum	Left Tibia	Right Tibia
Total nucleated cells (per c.mm.)	24,000	31,000	100,000	80,000	51,000	40,000	75,000	45,000	50,000
Erythroid cells (%) ..	10·5	11·5	1·00	1·5	5·0	3·0	19·5	15·0	10·0
Myeloid cells (%) ..	79·0	74·0	88·5	77·5	55·5	41·0	75·0	76·5	86·0
Lymphoid cells (%) ..	10·0	14·5	7·0	16·0	47·5	53·0	5·5	7·5	3·5
Monocytes (%) ..	0·5	—	3·5	5·0	2·0	3·0	—	1·0	0·5

* Note that samples from different sites show fair agreement.

with moderate accuracy. Since these eight counts were distributed almost uniformly throughout the age period no great loss of accuracy would result from this. The total nucleated cell count has generally been considered of little significance on account of the unknown degree of dilution of marrow with blood in the aspirate. In our experience with both normal and anaemic infants, however, the nucleated cell count has been reasonably uniform when samples from different sites are compared (Table 1).

Fig. 1 and Table 2 show that there is a considerable fall in the total nucleated cell count over the first 10 days, from 136,000 to 35,000 per c.mm., followed by a rise to above adult values from four weeks (108,000) to three months (201,000). These figures could be explained either on the basis of blood admixture occurring more readily at the fourth and ninth day punctures, or of a genuine difference in the sample. Blood dilution affecting particularly these two counts is unlikely. Furthermore, examination of the differential counts (Table 3)

TABLE 2

BONE MARROW FROM BIRTH TO 3 MONTHS

Number of Cases	0–24 hours 19	3–5 days 23	8–10 days 23	26–33 days 19	55–62 days 6	82–99 days 12
Total nucleated cells (thousands per c.mm.)	136 †(45-290)	56 (5-117)	35 (5-100)	108 (61-248)	180 (62-338)	201 (108-449)
Smear cells (per 100 cells that could be named)	14·6 (1-43)	13·4 (0-40)	19·6 (0-40)	25·3 (0-80)	16·1 (0-41)	14·0 (0-50)
Named cells (thousands per c.mm.)	121 (41-250)	50 (5-117)	30 (4·2-85)	91 (6-228)	157 (44-296)	186 (95-429)
Mitotic figures in normoblasts per 100 nucleated cells ..	0·49 (0-1·5)	0·22 (0-1·0)	0·01 (0-0·5)	0·14 (0-0·5)	0·38 (0-1·5)	0·19 (0-1·0)
Erythroid cells (%)* ..	40·0 (18·5-65)	15·3 (0-32)	8·0 (0-20·5)	6·8 (2·0-16)	14·8 (7·5-34)	16·0 (6·5-31·5)
Myeloid cells (%)* ..	46·4 (20-73)	60·6 (44-88)	50·0 (34-73)	31·1 (13-55)	36·6 (22-50·5)	36·8 (10-86)
Lymphoid cells (%)* ..	12·1 (2·0-22·5)	22·9 (7·5-58)	37·3 (20-64)	55·6 (43-84)	48·5 (15-61)	47·0 (4·5-83·5)
Monocytes (%)* ..	1·5 (0-3·0)	1·2 (0-3·0)	1·7 (0-3·0)	1·1 (0-2·5)	0·1 (0-0·5)	0·5 (0-2·0)
Erythroid cells (thousands per c.mm.)	48·6 (13-124)	6·99 (0-24)	2·8 (0-9·2)	6·3 (0·18-19)	22·3 (4·6-50·4)	29·5 (6·9-83)
Myeloid cells (thousands per c.mm.)	56·3 (17-108)	33·3 (1·7-79)	18·2 (3·3-62)	29·0 (4·3-82)	53·9 (15-97)	71·8 (11-172)
Lymphoid cells (thousands per c.mm.)	14·2 (2-44)	9·59 (1·8-30)	9·2 (2·2-27)	54·9 (4·4-162)	81·0 (15-181)	79·7 (9-135)
Monocytes (thousands per c.mm.)	1·9	0·6	0·4	0·8	0·1	0·1

† The mean of each group is given, with the range in brackets.
* The detailed distribution of the different types of cells is given in Table 3.

shows that the proportion of immature cells of the myeloid series is virtually unchanged, although admixture of blood large enough to cause these total changes would lead to a relative increase in the more mature myeloid cells at the expense of the primitive ones. A smaller but still significant drop of this kind was found by Shapiro and Bassen (1941).

From these considerations it is clear that variations in the total nucleated cell count of the marrow are significant, so that it becomes logical to express the numbers of the different types of cells in terms of their concentrations per c.mm. in the marrow. In spite of the relative inaccuracy of their measurement, since neither the total nucleated cell count nor the differential count is measured with great accuracy, experience with normal and abnormal infants has satisfied us that the best available measure of activity of the different haemopoietic tissues of the marrow, erythroid, myeloid and lymphoid, is provided by the concentrations of these cells in marrow aspirate.

Smear Cells. The presence of large numbers of smear cells in the marrow of normal and abnormal adults and children has been ignored by the standard authorities (Leitner, 1949; Israëls, 1948) probably because no interest has been taken in absolute values of the marrow cells. Examination of infants' marrow showed, however, a markedly variable number of unrecognizable smear cells.

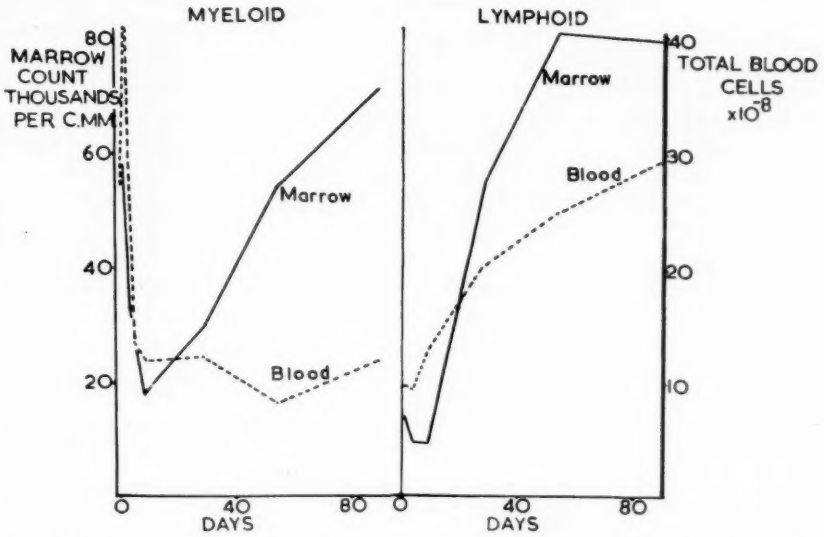

FIG. 2.—The concentration of myeloid and erythroid cells in the marrow, and the total number of myeloid and lymphoid cells in the blood, from birth to 3 months. (For interpretation see text.)

TABLE 3
BONE MARROW FROM BIRTH TO 3 MONTHS

	0–24 hours	3–5 days	8–10 days	26–33 days	55–62 days	82–99 days
Number of cases	19	23	23	19	8	12
Haemocytoblasts	0	0	0	0	0	0
Proerythroblasts	0–1 (0·5)	0–0·5	0	0–0·5	0–1 (0·5)	0–1 (0·5)
Normoblasts, early	0·5–9 (3·0)	0–2·0 (0·5)	0–0·5	0–1·5 (0·5)	0·5–10 (2·0)	0–3·5 (1·5)
,, intermediate	5–19 (10)	0–8·5 (4·0)	0–5 (1·5)	0–3·5 (1·5)	1·5–13 (6·0)	1·0–7·0 (4)
,, late	18–41 (26)	0–23 (10)	0–15 (6)	1–15 (5)	4·5–13 (6·5)	2·5–22·0 (10)
Myeloblasts	0·5–2·0 (1·0)	0–2·5 (10)	0–3 (1·0)	0–2 (0·5)	0·5–5·0 (1·0)	0–4 (1·5)
Promyelocytes	0·5–5·0 (1·5)	0·5–9·0 (3·0)	0·5–7·0 (2·0)	0–4 (1·0)	0–3 (1·0)	1·5–5 (2·0)
Myelocytes, neutrophil	1–9 (4)	3–15 (7·5)	1–11 (4)	1·5–13·5 (4·5)	2–12 (5)	0·5–16 (5)
,, eosinophil	0–2·5 (1·0)	0–2·0 (1·0)	0–2 (1·0)	0–1	0–2 (0·5)	0–2 (0·5)
,, basophil	0–0·5	0–0·5	0–0·5	0	0	0
Metamyelocytes, neutrophil	4·5–25 (14)	4–32 (25)	7–35 (18)	4–31 (10)	3–17·5 (12)	3–33 (11)
,, eosinophil	0–2·5 (1·0)	0–2·5 (1·0)	0–2 (1·0)	0–1	0–2 (1·0)	0–2 (1·0)
,, basophil	0–0·5	0–0·5	0–0·5	0	0–0·5	0–0·5
Polymorphs, neutrophil	10–40 (22)	15–38 (20)	11–45 (20)	2–27 (12)	8–19 (15)	2–24 (15)
,, eosinophil	1·0–3·0 (1·5)	0·5–3·0 (1·0)	0–2 (1·0)	0–1	0–2 (1·0)	0–2 (1·0)
,, basophil	0–0·5	0–0·5	0	0	0	0
Lymphoblasts	0–0·5	0–0·5	0–3·5 (0·5)	0·5–3 (2·0)	0–1·5 (0·5)	0–5·5 (2·0)
Lymphocytes	4–22 (12)	8–36 (23)	20–62 (37)	27–73 (54)	15–60 (48)	31–81 (47)
Plasma cells	0	0	0	0	0	0
Monocytes	0–2·5	0–3 (1·0)	0–3 (1·0)	0–6·5 (1·0)	0–0·5	0–1 (0·5)

* Differential count (percentages). The range is given with average values in brackets.

An average of about 24 of these were present to the standard count of 200 recognizable cells, with individual variations from none to 100. No correlation could be found between the degree of smearing and the amount of suction necessary to withdraw a specimen, the marrow cellularity, or the age of the infant.

This necessarily gives rise to a background of about 5,000-15,000 unrecognizable cells per c.mm. in each specimen. This count seemed to parallel fairly closely the absolute number of lymphocytes present in an individual marrow specimen, and in view of the known fragility of lymphocytes in blood films, it would seem that these smear cells are probably mainly lymphocytes. Since however their nature remains doubtful they have been excluded from further consideration.

The Marrow Differential Count. The range of values for each type of cell and the mean values are given in Table 3. These are published mainly to give a tentative set of values for an age group which has been little dealt with in the literature. Since the number of samples at each age group is not large the range of normals may well be wider than that given.

The cell morphology was identical with that seen in normal adult marrows apart from an occasional macronormoblast in the specimens taken on the first day. No megaloblastic erythropoiesis was seen in any of the marrows examined. The haemoglobinization and nuclear maturation of the normoblasts followed a normal pattern.

ERYTHROID CELLS. At birth the marrow contains on an average 40% erythroid cells. These are rapidly reduced to about 8% during the first 10 days of life. Thereafter they stay relatively constant for about three weeks and then increase to about 15% during the next two months. The striking fall in the proportion of erythroid cells in the first few days of life has been previously noted. Shapiro and Bassen (1941) found a mean of 32% on the first day and 12% on the seventh day for the 35 babies which they examined, agreeing well with our figures; their work was carried out on sternal marrow. Tecilazic (1935) also studied the changes during the first few days of life using tibial marrow: on the first day the erythroid percentage was 66% and on the seventh day 40%, showing a similar but less marked post-natal fall, although the proportions of erythroid cells are much higher than we have found. Lamy *et al.* (1939) conclude that during the first few days of life there are 35%-50% erythroid cells and that during the first week they fall to 25%-35%. Similarly Veeneklaas (1938) records marrow data of a group of three infants under 14 days and finds 12% erythroid cells; although the ages of these infants are not recorded the text suggests an age of between 7 and 14 days. Glaser, Poncher and Limarzi (1948) found a rather low proportion (23%) of erythroid cells during the first two days of life, but agree that there is subsequently a fall followed by a rise.

These changes during the early months of life are seen even more clearly if the total erythroid cells per c.mm. are calculated. These figures show a fall from 46,000 per c.mm. at birth to less than 3,000 per c.mm. at day 9, and then a steady rise from the end of the first month to nearly 30,000 at 3 months (Table 2).

The marrow reticulocytes were also investigated but gave no additional information, for they ran parallel to, but a little higher than, the blood reticulocytes at each age period. The percentage of mitotic figures in the early normoblasts gave a good index of the erythroid activity, for this mitotic activity paralleled the changes in total erythroid count.

The significance of these changes in erythropoietic activity is discussed in detail in Part II of the paper.

MYELOID CELLS. On the first day of life myeloid cells form 46% of the marrow nucleated cells. During the next few days the *percentage* of these cells increases but eventually stabilizes at about 35% of the marrow cells. These findings agree closely with those of Tecilazic (1935), Veeneklaas (1938), Lamy *et al.* (1939), Shapiro and Bassen (1941) and Glaser *et al.* (1948).

The *concentration* of myeloid cells in the marrow falls from birth to day 9 and then rises steadily until the third month. Fig. 2 shows the relationship between the number of myeloid cells in the marrow and in the blood. The latter, expressed as total circulating myeloid cells (Table 4), show a sharp fall after the first day, thereafter remaining at the lower level. Fig. 2 also shows that the fall of the blood myeloid cells after the first day corresponds to the fall in marrow myeloid cells, but that the subsequent rise in marrow myeloid cells produces in the blood no corresponding increase. In a few infants who have been excluded from this series because they developed minor infections, the marrow myeloid cells were increased above normal values although there was no blood leucocytosis. This finding requires further investigation, but it is tentatively suggested that the rise in the marrow myeloid cells is required to provide cells not only for the circulating blood but also for minor inflammatory reactions throughout the tissues of the body.

TABLE 4

TOTAL CIRCULATING LEUCOCYTES FROM BIRTH TO 3 MONTHS (MEANS OF 105 EXAMINATIONS)

	Cord	2–24 hours	3–5 days	8–10 days	26–33 days	55–62 days	82–99 days
Total blood myeloid cells $\times 10^{-8}$	27·2	41·7	13·4	11·6	12·2	8·6	11·7
Total blood lymphoid cells $\times 10^{-8}$	9·3	9·5	8·8	12·7	20·0	24·7	29·3
Total blood monocytes $\times 10^{-8}$	3·3	4·4	2·3	2·7	2·9	1·8	2·7

LYMPHOID CELLS. The marrow lymphoid cells show a steady rise, both in percentage and in number per c.mm., until from the fourth week they form 50% of the marrow cells. This closely parallels the course of total blood lymphoid cells (Fig. 2 and Table 4). Since the concentration of lymphoid cells per c.mm. in the marrow is far greater than in the blood, and since the marrow shows the presence of many lymphoblasts, the marrow must at this stage be a major site for lymphocyte formation, even if this function is largely lost before adult life.

MONOCYTES. We have been unable to confirm the neonatal monocytosis reported by Lamy *et al.* (1939) and in fact have found a steady fall in the total number of monocytes in the blood. The number of monocytes in the marrow also falls over these three months, but these changes are probably not significant on this small number of counts.

Myeloid/Erythroid Ratio. This value has been widely adopted as a measure of myeloid or erythroid activity. In the infant it is of little value, and can in fact be misleading since it takes no account of the large changes which occur both in the total nucleated cell count and in the proportion of lymphocytes.

Summary and Conclusions

The normal marrow picture from birth to 3 months has been defined by examining 102 specimens of tibial marrow. Large changes are seen in the cellularity of the marrow during this phase, an initial drop from a mean of 136,000 per c.mm. on the first day to 35,000 on the ninth day, and a subsequent steady rise to 201,000 at three months. In view of these changes the total erythroid/myeloid and lymphoid counts per c.mm. provide more accurate indices of the different types of haemopoietic activity than do the percentages of these cells or the myeloid/erythroid ratio.

The marrow erythroid count at birth is about 41,000 per c.mm.; this falls to 2,800 at the ninth day and subsequently rises again to an average of 25,000 from two to three months: these changes are discussed further in Part II of this paper. The marrow myeloid count shows a similar fall at the end of the first week and a subsequent rise despite the constancy of the total number of myeloid cells in the circulation. The marrow lymphoid count shows a steady rise over the period studied, which parallels the rise in blood lymphocytes.

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APLASIA OF THE BONE MARROW: A NEW CAUSE OF THE VON JAKSCH SYNDROME

BY

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Almost simultaneously von Jaksch, Hayem and Luzet described a disease characterized by anaemia with numerous immature red and white cells in the peripheral circulation and marked enlargement of the liver and spleen. The nutrition of patients with this disease had in most cases been inadequate. They often also had rickets and infections. Spontaneous recovery was the rule, but it took from one to one and a half years. Because of the many immature cells in the blood, the syndrome was called pseudoleukaemic anaemia. Nowadays this syndrome is not considered to be a separate entity and the symptoms, although to a milder degree, may be observed in anaemias and infections of various origin. Cooley's conception describes present day opinion fairly accurately: 'The terms von Jaksch anaemia and Hayem-Luzet syndrome have served their purpose and can be discarded. Nothing worthwhile has come out of that particular wastebasket—and if it accomplishes anything now, it is to encourage laxity in diagnosis.' I think I have after all been able to find something of value in this 'wastebasket'.

There are children today, although they are rare, who present all the symptoms to a marked degree. Till now no satisfactory explanation for its development has been put forward. I was able to observe two patients both with severe aplasia of the bone marrow, and I am of the opinion that this may very well be the cause of the syndrome.

Case Reports

Case 1.—C.S., born on August 12, 1947, was admitted to the hospital on February 7, 1949, and discharged on August 4, 1949.

This 1½-year-old boy was born spontaneously, at full term, after a normal pregnancy, with a birth weight of 3,100 g. He had been breast fed for two months and had then been fed on milk, water, flour and sugar until the age of 9 months. By that time potatoes and vegetables were added; no fruit, no cod liver oil and no vitamins A, C or D were given. The teeth erupted at the age of 1 year, but the child could not yet sit up alone at the time of admission. From the age of 6 months he had had an upper respiratory infection about every month.

The parents and four other siblings were healthy. The father was a day labourer, the family living in poor circumstances.

Physical examination showed the child to be in a good nutritional condition, interested in his surroundings. The height was 71 cm., weight 8,480 g., temperature 37·6° C. There was a caput natiforme, purulent discharge from the nose, and there were two lower incisors. Many enlarged lymph nodes were palpable behind the sternocleidomastoid muscle. A rachitic rosary and Harrison's grooves were present. The liver was palpable two fingerbreadths below the costal margin; the spleen almost reached the iliac crest. Epiphyseal swellings of the extremities were present. Otherwise nothing abnormal was found. Urine and faeces were normal. Serological reactions for syphilis and cutaneous tests for tuberculosis were negative. The galactose tolerance test was normal. There were no signs of haemolysis, no urobilinuria or bilirubinaemia. There was no Rh or ABO antagonism between the parents.

BLOOD EXAMINATION. This gave haemoglobin 60%, erythrocytes 3·36 million per c.mm.. slight anisocytosis, poikilocytosis, polychromasia. The Price-Jones curve was within normal limits. Reticulocytes were 6%, thrombocytes 142,280 per c.mm., leucocytes 19,200 per c.mm. (myelocytes 5, metamyelocytes 4, band forms 15, polymorphonuclear neutrophils 36, monocytes 5, lymphocytes 35, erythroblasts 30). The blood sedimentation rate was 20 mm., the coagulation time was 2 minutes 45 seconds, the bleeding time 3 minutes 45 seconds. The blood phosphorus was 2 mg. per 100 ml., calcium 8·2 mg. per 100 ml., phosphatase 136 units, ascorbic acid 0·2 mg. per 100 ml.

BONE MARROW EXAMINATION. In the bone marrow smear numerous reticular cells were seen, whereas the bone marrow elements, such as myelocytes and erythroblasts (Fig. 1) were scarce. (These cells were fairly

numerous in the peripheral circulation.) Bone marrow punctures were performed in the sternum, the ilium and the malleoli. Microscopic examination of a tibial bone marrow sample showed a picture similar to that of the smear, i.e. scarcity of bone marrow elements. Reticular elements were visible, but almost no myelocytes and no erythroblasts. As far as they were seen, they were mostly situated in the outlying part of the bone marrow bordering on the cartilage (Figs. 2 and 3).

TREATMENT. The patient was put on a diet rich in vegetables, fruit and proteins, while 300 mg. ferrous lactate, 50 mg. ascorbic acid, 1,000 I.U. vitamin D and 3,600 I.U. vitamin A were given daily. When it appeared that the red blood picture did not react to treatment injections of liver extract were given, followed by folic acid, 15 mg. daily. Ultra-violet irradiation was instituted twice weekly from the 64th day of the child's stay in hospital or he was placed outdoors when the weather permitted; 126 days after admission the adenoids were removed.

COURSE. The general condition improved very slowly and gradually during the six month's stay in hospital. Nose and throat infections occurred a few times. His rickets were cured rapidly. Towards the end of his stay the child could stand and had six teeth. He weighed 9,630 g. Phosphorus and phosphatase values were normal. On June 29, 1949, the calcium was 9·4 mg. per 100 ml., phosphorus 6 mg. per 100 ml. and phosphatase 18 units. The liver and spleen had gradually become smaller, and were only just palpable at the time of discharge. The values for haemoglobin and red cells, however, remained practically constant (Fig. 4). There was a slight reticulocyte crisis 30 days after admission, but after another month the number had returned to normal. After six weeks a few erythroblasts were found in the peripheral blood; after seven weeks the white blood picture had become normal: leucocytes 7,900 (eosinophils 2, polymorphonuclear neutrophils 28, lymphocytes 65, monocytes 5).

Three months after admission a slight increase of the myelocytes and erythroblasts in the bone marrow was noted, and remained practically unchanged until the end of the hospital stay. Microscopic examination of a biopsy specimen of tibial bone marrow obtained a few days before discharge revealed a slight increase of the specific cells of the marrow, but it was still characterized by a preponderance of reticular cells and scarcity of myelocytes and erythroblasts.

On December 21, 1950, the child was re-examined and found to be in excellent condition. He was now 3 years old; height was 94 cm., weight 15 kg. The liver and spleen could not be palpated. Blood values were as follows: Hb. 74%, red cells 4·68 m. per c.mm., reticulocytes 0·2%, leucocytes 11,100 per c.mm. (eosinophils 2, polymorphonuclear neutrophils 33, lymphocytes 62, thrombocytes 272,080 per c.mm.). Bleeding time was 1 minute 30 seconds and coagulation time 2 minutes 30 seconds. The bone marrow had numerous cells and did not differ from normal bone marrow of that age.

Case 2.—I had occasion to see a second case showing the same clinical syndrome which, to save space, is not described fully. Treatment in this case consisted of giving a complete diet. In the course of a few months the symptoms disappeared. When this patient was first seen the bone marrow was atrophic and contained chiefly reticular cells. In the smear this preponderance was quite remarkable (Fig. 5). A biopsy specimen showed that red and white cells were still being formed on the border line of cartilage and bone, but elsewhere the marrow spaces were empty, except for reticular cells (Fig. 6). Four months after the beginning of treatment the blood picture had become normal and the liver and spleen were still palpable. A year after treatment these organs were no longer palpable and the bone marrow had become normal (Fig. 7).

Other Cases.—Bone marrow smears of a patient who had been in hospital 16 years previously with the same history and identical symptomatology were also characterized by a scarcity of plastic elements and abundance of reticular cells. At that time we were unable to diagnose this picture and ascribed these findings to poor technique. In this patient, and in six others seen in the course of the intervening years presenting identical symptoms and recovering in a few months under a complete diet, we did a new bone marrow biopsy. In all these patients the bone marrow was normal.

Discussion

Clinically these two patients presented the typical picture of von Jaksch pseudoleukaemia. The previous history revealed deficient nutrition and recurrent infections. They both had rickets. Besides hepatosplenomegaly numerous immature red and white cells were found in the blood. In the first patient a rapid reaction to treatment with iron, liver extract or folic acid was neither expected nor seen, but there was a slow, steady improvement, as is also seen when infections become less frequent and when an adequate diet is given, as was observed in the second patient.

An entirely new aspect of the syndrome is the lesion of the bone marrow. It is difficult to determine what really causes the bone marrow aplasia. Infections, deficient nutrition and rickets, separately or together, do not always lead to the development of the von Jaksch syndrome. It is not known whether or not the bone marrow is involved in these cases, and considering the rarity of the simultaneous occurrence of malnutrition, infections and rickets in a country where infant welfare is well organized, it is hard to establish this definitely. A connexion between this bone marrow aplasia and the von Jaksch syndrome is highly probable. The coincidence of only slight improvement of the bone marrow aplasia with a disappearance of the syndrome may lead to the conclusion that this syndrome only develops fully when there is a marked aplasia of the bone marrow and is therefore rarely seen.

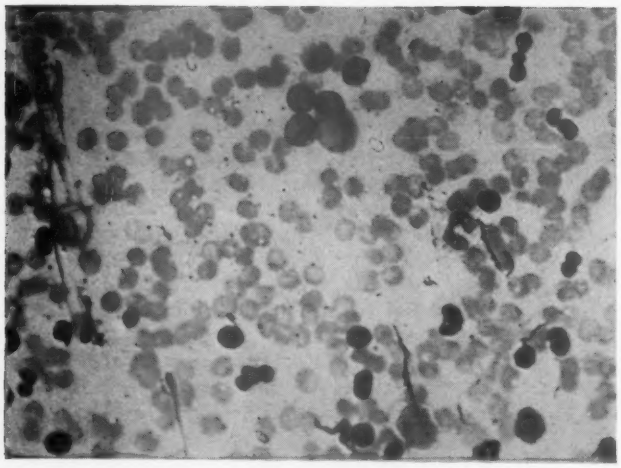

FIG. 1.

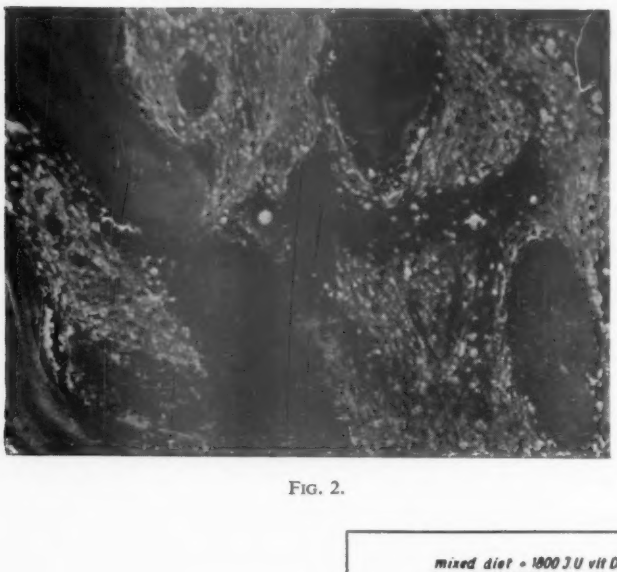

FIG. 2.

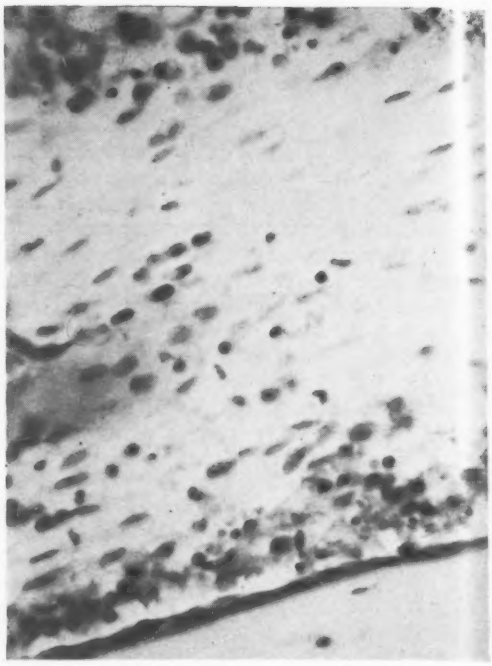

FIG. 3.

FIG. 1.—Case 1. Bone marrow smear showing numerous reticulum cells, very few erythroblasts or myelocytes.

FIG. 2.—Case 1. Section of tibia marrow showing marked aplasia.

FIG. 3.—Case 1. Section of tibia marrow showing aplasia and myelocytes and erythroblasts only at the edges near the bone.

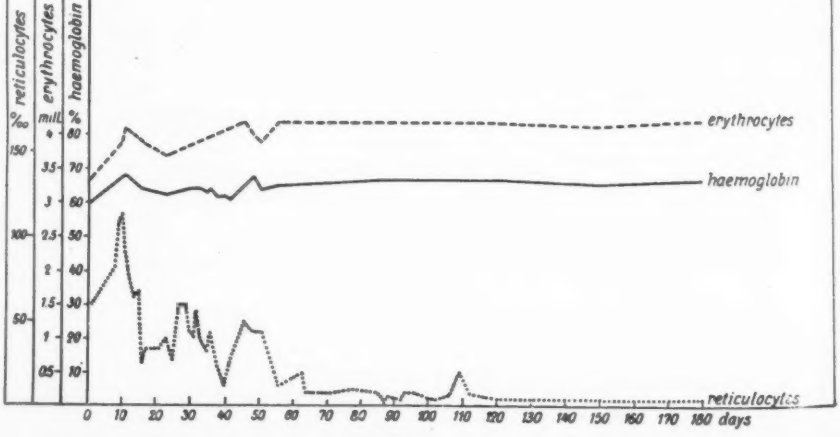

FIG. 4 —Case 1. Constant levels of erythrocyte and haemoglobin values regardless of various treatments.

FIG. 4.

A lesser degree of aplasia might occur without or with only slight enlargement of the liver and spleen. Once my attention was drawn to this fact, I saw several cases with slight aplasia of the bone marrow, especially in cases of anaemia. In these cases the anaemia was of many months standing and was microcytic and hypochromic. There were no changes in the white cells, but erythroblasts were regularly seen in the peripheral circulation. The bone marrow was normal so far as the white cells were concerned, but there were more reticular cells than normally seen, while at the same time the red system presented a scarcity of elements.

Rohr (1949) advanced the hypothesis that immature cells always have their origin in extramedullary foci. It is not known whether this holds true for all cases and for all degrees in which the phenomenon occurs. Important arguments in favour are the following. From present day knowledge it is assumed that the bone marrow circulation is a closed system whereas the spleen has an open system. The liver haemopoiesis is partly intravascular. During foetal life, when spleen and liver participate in haemopoiesis, immature elements in the peripheral circulation are numerous. In leukaemia with considerable enlargement of the spleen and liver the number of cells in the blood is high, and irradiation of the spleen causes a rapid decrease of cells. In aleukaemic forms marked spleen and liver enlargement are absent. This theory tends to explain the 'hiatus leukaemicus'. We did not perform either liver or spleen biopsy in our very youthful patients, which might have furnished data on the presence of haemopoietic foci in these organs. The scarcity of immature cells in the bone marrow and their abundance in the blood make it seem probable that these cells originated in extramedullary foci, and in cases with marked hepatosplenomegaly it seems likely that these are the site of origin, the more so as disappearance of the immature cells from the peripheral circulation is found simultaneously with a decrease in size of these organs. Extensive haemopoiesis in the liver and spleen were found at necropsy of these patients. Since the disappearance of immature cells from the circulation and a decrease of hepatosplenomegaly

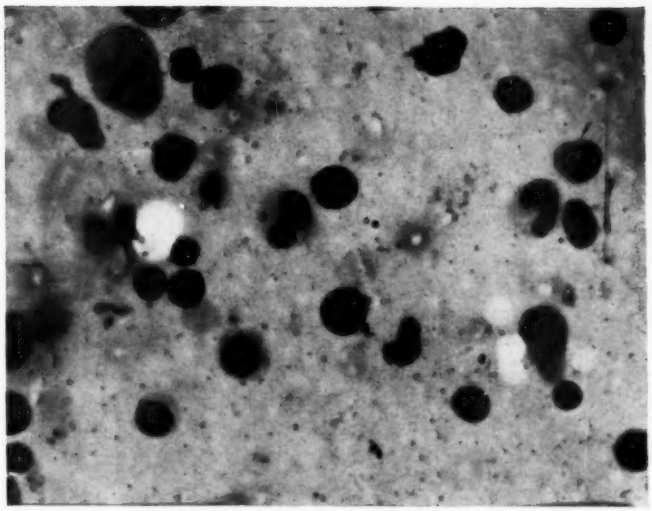

FIG. 5.

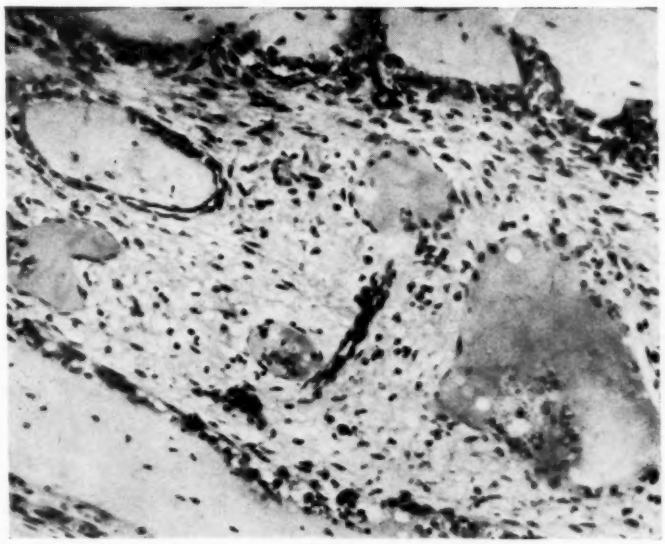

FIG. 6.

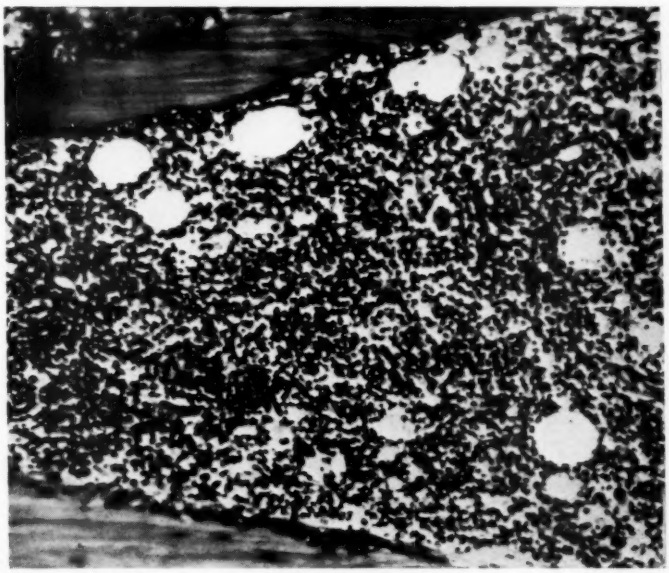

FIG. 7.

FIG. 5.—Case 2. Bone marrow smear showing prevalence of reticulum cells, scarcity of myelocytes and erythroblasts.

FIG. 6.—Case 2. Section of tibia marrow showing central aplasia and erythroblasts and myelocytes in the periphery.

FIG. 7.—Case 2. Section of tibia marrow one year later. A state of normal activity has returned.

coincide with improvement in the atrophied bone marrow a connexion between the three symptoms is self-evident. Considering the large reserves possessed by the bone marrow, a slight improvement of the haemopoietic function may make extramedullary haemopoiesis superfluous.

During various infections in young children a few immature cells are found in the blood stream, and haemopoietic foci may be encountered in the liver and spleen without any impairment of the haemopoietic function of the bone marrow.

It is well known that the action of different infectious or toxic noxae on the bone marrow may be followed by a decrease in the number of one or more cell types. It seems, therefore, highly probable that in cases such as those described above, the lesion of the bone marrow being severe and needing a long time for its repair, cell production is taken over by the liver and spleen, which possess this capacity to a heightened degree at this early age.

The sequence of events might be as follows: recurrent infections and deficient nutrition; reaction of the bone marrow with a scarcity of plastic elements; in case of failure of the bone marrow to recuperate quickly enough, vicarious functioning of the liver and spleen; with discontinuance of recurrent infections and deficient nutrition the haemopoietic function of the liver and spleen is gradually taken over by the bone marrow.

In our patients the anaemia was microcytic and hypochromic. In the literature a colour index above 1 is sometimes mentioned. This is not surprising, as the anamnesis of the von Jaksch syndrome reveals deficient nutrition, and the type of this deficiency determines whether the subsequent anaemia will be macrocytic or microcytic, hyperchromic or hypochromic. The syndrome is rarely seen nowadays as compared with a few decades ago, because in general nutrition has markedly improved.

Summary

Two patients with a well defined von Jaksch syndrome presented hepatosplenomegaly, anaemia and numerous immature red and white cells in the blood stream, with severe aplasia of the bone marrow.

In smears, as well as in biopsy material of the bone marrow, reticular cells were found almost exclusively.

Both patients had had a deficient diet and numerous infections and both had rickets. With a normal diet the immature cells disappeared from the blood, the liver and spleen returned to normal size in the course of some months, while at the same time the aplasia of the bone marrow improved. A normal bone marrow was found in both patients one and three-quarter years and one year respectively after treatment.

Based on these observations we regard it as possible and even probable that the von Jaksch syndrome arises as a sequence of, and is therefore secondary to, aplasia of the bone marrow.

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THE SCHÖNLEIN-HENOCH SYNDROME AND COLLAGEN DISEASE

BY

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The clinical manifestations of the Schönlein-Henoch syndrome as described in articles by Gairdner (1948), Davis (1948) and other writers, are a typical exanthem, colic, haematuria, articular and periarticular swellings, and a liability to develop nephritis. Gairdner drew attention to the possible relationship between this syndrome, acute nephritis, rheumatic fever and polyarteritis nodosa.

It is proposed to record 35 cases occurring in children between 4 and 13 years old who have been in-patients at Alder Hey Children's Hospital, Liverpool. For convenience these 35 cases will be considered in two groups: Group A, comprising 14 cases admitted between 1944 and 1947, and Group B, comprising 21 cases admitted between 1948 and the end of 1950. Those in the second group were more extensively investigated and their progress has been closely followed.

In addition, it is proposed to describe four atypical cases which have features in common with the syndrome and also appear to be diseases of the collagen system.

Clinical Manifestations of the Typical Cases

At the time of admission to hospital the typical exanthem was present in 11 of the 14 earlier cases: in the remaining three abdominal colic was the initial symptom and the rash appeared from one to 21 days later. Of the 21 cases in Group B the rash was present at the onset in 20 and occurred subsequently in the other case. Of the total 35 cases in both groups, 19 patients had complained of a sore throat before admission to hospital and one child had had ulcerative stomatitis. Twenty-six children had abdominal colic; all had anorexia and were drowsy or listless. Blood was passed per rectum in 11 cases, and in one of these an acute abdominal condition had been diagnosed on admission and laparotomy performed. Amongst the earlier cases (Group A) only three had joint manifestations, whereas of the 21 more recent cases (Group B) 17 had pain and swelling around joints, the ankles, knees and wrists being most commonly affected. A puffy swelling of the backs of the hands was frequently observed.

The rash in all cases was distributed over the extensor surfaces of the elbows, the dorsa of the feet and ankles and on the buttocks. Red macules appeared early varying in size and frequently tending to spread: they later became darker in colour, almost semi-necrotic, and eventually faded leaving brown staining which was visible for many days, especially on the front of the ankles. In more than half of the recent cases a small, raised, white patch was noticed on the prominent upper part of the antihelix (Fig. 1); this later became reddened and necrotic, finally leaving a brown scab. The phenomenon did not seem to be directly related to pressure of the head on the pillow.

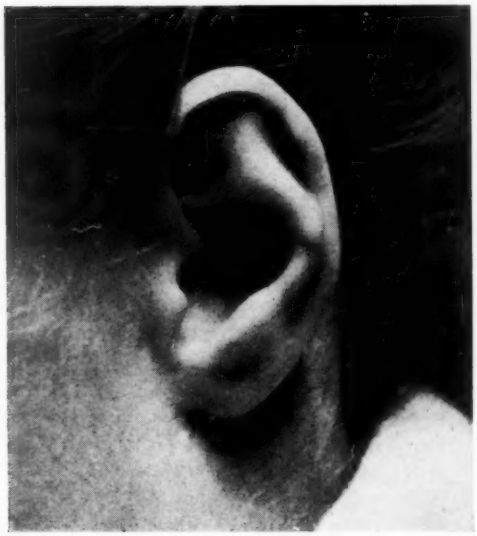

FIG. 1.—Papule on antihelix.

Aetiological Factors

Of the 21 later cases (Group B) a careful history was taken to explore the pathogenesis.

The possibility of a food sensitivity was investigated but in no instance was there any definite indication. One child was thought by the relatives to be ' sensitive ' to grapes, but she was discovered eating some after a visiting day and there were no untoward effects. Skin tests (Bencard) were carried out in five cases: one child gave a positive reaction to potato and another to tomato. The former child had several relapses of the condition which were not prevented by the exclusion of potato from her diet, and the other ate tomatoes while in hospital without, apparently, any ill-effects.

Special consideration was given to the suggestion that there might be an acquired sensitivity to sulphonamides, the subsequent exhibition of which might provoke the syndrome. Only two children had a history of having received sulphonamides shortly before admission to hospital and in one of these the drug had been given only after the rash had appeared. Sulphonamides given during the observed course of the illness did not precipitate a relapse of the syndrome nor seem to lessen the symptoms.

The relationship between the onset of the syndrome and an infection with a haemolytic streptococcus was suggestive as this organism was isolated from the throat swabs of 15 of the 21 cases in Group B; some of these organisms were typed but the findings lacked uniformity, types 6, 12 and 25 being encountered in the three cases in which this investigation was carried out. Half the cases in Gairdner's series were also associated with haemolytic streptococcal infections.

A particularly close relationship was found between throat infections and relapses of the condition. Seven children had recurrences of the rash: from three of these children, who each had two relapses, haemolytic streptococci were cultured at the time of each relapse, but this organism was not found during the symptom-free intervals. The interval between the onset of the sore throat and the appearance of the rash was noticeably shorter in the recurrences than in the original attack. This occurred in six of Gairdner's 12 cases and might be claimed as support for the theory that the condition is of an allergic nature; the alternation of symptoms, which was observed in those who had recurrences, might also support such a supposition.

Pronounced histamine sensitivity was found in some cases, a solution of histamine in as great a dilution as 0·0003 mg. ml. producing a positive skin reaction.

Treatment

Dietetic measures were directed towards the exclusion of substances to which skin tests have positive results, but without lessening the severity of the symptoms or, apparently, preventing recurrences.

When evidence of a throat infection was present, or when haemolytic streptococci were isolated from the throat swabs, courses of systemic penicillin were given. Three patients, in whom the syndrome recurred more than once and was associated with haemolytic streptococci in the throat swabs, were submitted to tonsillectomy. Two of these children had no further attacks of the syndrome after this operation.

Certain anti-histamine drugs (benadryl, antistin, anthisan, phenergan and thephorin) were used, variously, in 18 of the 21 cases in Group B without benefit.

Prognosis

Of the 21 cases which have occurred since 1948 (Group B) all are alive and appear well. Recurrences have, however, been frequent and one child has had five within two years. Albuminuria has been the commonest sequel. This has occurred in three cases since other manifestations ceased. One child had albuminuria for 18 months after the onset of the condition but subsequently her urine has remained clear: at no time has there been a rise in blood pressure or nitrogen retention. None of these children has developed clinical evidence of carditis or any change in the electrocardiogram.

Four Atypical Cases

All of the 35 cases described above conformed to a similar pattern and were of a comparatively mild nature. The Schönlein-Henoch syndrome has, however, been described as one of a ' family of diseases ', another member of the family being polyarteritis nodosa. Harkavy (1950) has linked together lupus erythematosus, dermatomyositis, polyarteritis nodosa and the Schönlein-Henoch syndrome with nephritis, as presenting common features referable to disease of the collagen system. Four children, in addition to the 35 described, presented clinical manifestations of the Schönlein-Henoch syndrome but later developed graver aspects of collagen disease.

Case Reports

Case 1. Rodney McM., aged 5½ years, was admitted to Alder Hey Children's Hospital with a purpuric eruption on the face, palms of the hands and buttocks.

There was a history of a morbilliform rash two months previously and he had also had attacks of asthma and bronchitis. The onset of the exanthem was accompanied by prostration, swelling of the wrists and knees, haematuria and severe colic with blood-stained diarrhoea. The skin over the sacrum became gangrenous (Fig. 2) and albuminuria developed. The child remained very ill for 14 weeks and more than once seemed likely to die; after a blood transfusion, however, his condition slowly improved. A muscle biopsy showed diffuse inflammatory changes, frequently perivascular in distribution, with occasional areas of necrosis of the walls

FIG. 2.—Gangrenous area over sacrum.

of small vessels (Figs. 3 and 4). No nodules were found, there was no evidence of peripheral neuritis, and the optic fundi showed no changes; there was, however, considerable emaciation with persistent tachycardia and recurrent attacks of severe abdominal pain. The urine eventually cleared and the skin healed. The

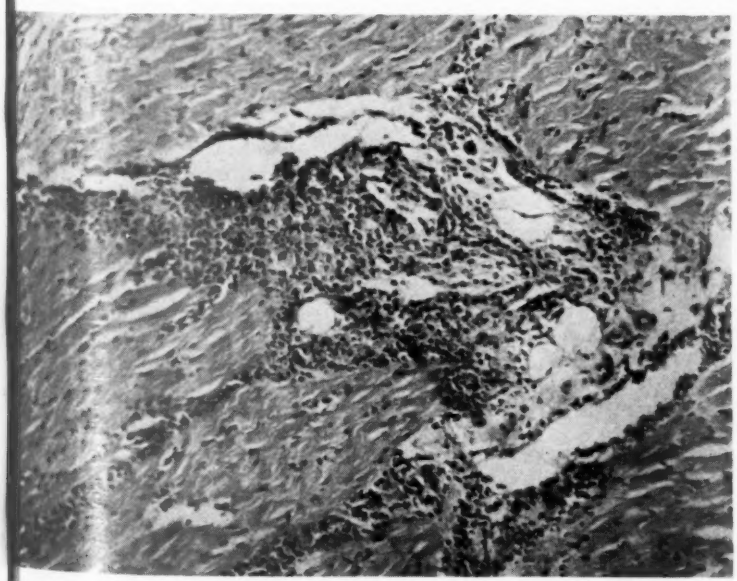

FIG. 3.—Muscle biopsy (H. and E. × 125) showing diffuse inflammatory infiltration.

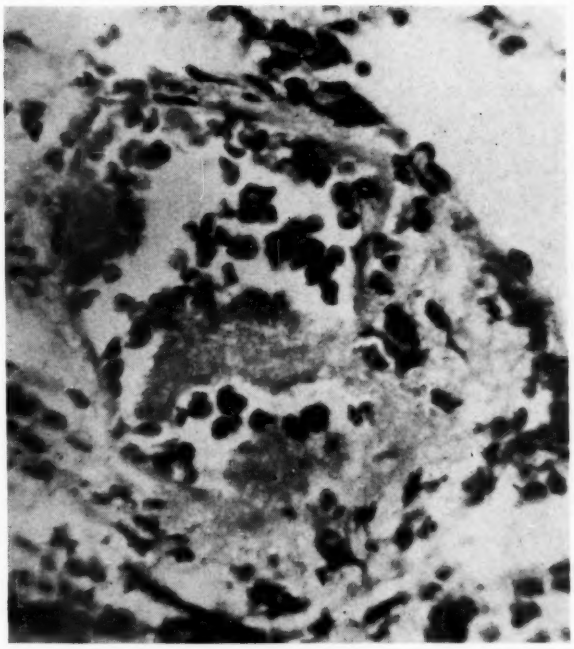

FIG. 4.—Muscle biopsy (H. and E. × 600) showing partial necrosis of vessel wall and overlying thrombus.

child was discharged after five months in hospital when his condition had considerably improved. He has been observed as an out-patient for a year and continues to make good progress; the skin now appears normal except for a scar over the sacrum.

This child presented as a severe case of the Schönlein-Henoch syndrome, but, as shown in Figs. 3 and 4, vascular involvement indicates a relationship to polyarteritis nodosa. Werlhof's purpura haemorrhagica has been excluded by a normal blood platelet count. This case resembles two of the three cases described by Sheldon (1947) in which there were purpuric patches with black haemorrhagic centres which eventually left permanent scars on the buttocks; these he called purpura necrotica.

Case 2. Jeanette D., aged 15 years, was admitted to Alder Hey Children's Hospital with a history of swelling of joints and a purple rash on the arms and legs, both of which manifestations had been present from time to time during the previous three years. At the age of 12 years she had been diagnosed as a case of erythema nodosum and her joint symptoms had been attributed to acute rheumatism. A skin biopsy, however, then showed the appearances of disseminated lupus erythematosus. Latterly she had been found to have tender nodules on the forearms and also on the chest wall. A more recent muscle biopsy showed panarteritis with thrombosis and

recanalization (Fig. 5), together with cellular infiltration of the vessel walls.

The urine was consistently normal and there was no clinical or electrocardiographic evidence of carditis.

This child showed an extensive collagen involvement and the histological evidence supports the theory that disseminated lupus erythematosus and polyarteritis nodosa may co-exist. A similar case has been described in the 'Case Records of the Massachusetts General Hospital' (Mallory, 1938) and this relationship has also been stressed by other writers, including Banks (1941), Krupp (1943) and Harkavy (1950).

Case 3. Beryl R., aged 9½ years, was admitted to Alder Hey Children's Hospital with a widespread rash over the trunk and limbs resembling papular urticaria (Fig. 6). This rash changed rapidly in configuration, being at times indistinguishable from erythema marginatum. Abdominal colic and haematuria were present from the onset and recurred eight times in 12 months. It was noticed that the haematuria was most severe when the rash was extensive and at these times the child was drowsy and irritable. The blood sedimentation rate remained consistently very high, figures of the order of 60 and 120 mm. (Westergren) in the first hour being recorded. There were no joint manifestations and the heart sounds remained normal, and there was no abnormality in the electrocardiogram. A muscle biopsy did not show any abnormality of the larger vessels. It was found that there was a marked sensitivity to histamine, a positive skin test being obtained with a solution of 0·0003 mg. ml. This was the only case in the whole of the series that showed any response to the antihistamine drugs: it was found that phenergan, 25 mg. t.d.s., lessened her symptoms.

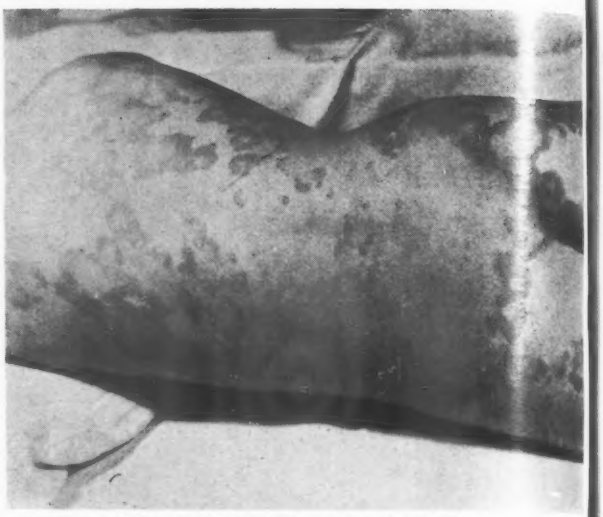

FIG. 6.—Widespread eruption (Case 3).

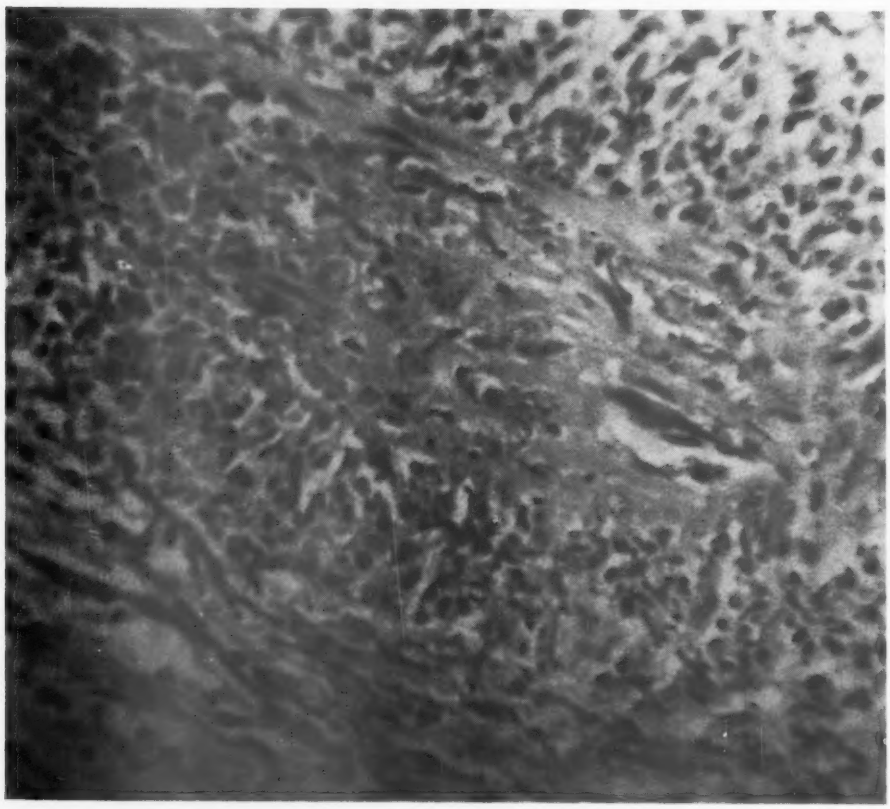

FIG. 5.—Muscle biopsy (H. and E. ×750) showing panarteritis with thrombosis and recanalization.

Two years after the onset of her illness the child is still being observed as an out-patient, and the rash still appears at intervals, although to a less marked degree; she also has a persistent albuminuria.

Although in this case the rash was not typical of the Schönlein-Henoch syndrome, its coincidence with abdominal pain and haematuria suggests a relationship with that condition. There were, moreover, many recurrences and at one and the same time she presented the urinary findings of nephritis and a rash then conforming to the marginal erythema of acute rheumatism.

Case 4. Brian J., aged 13 years, was admitted with a rash on the front of the legs which first resembled erythema nodosum, but later faded and was replaced by a rash similar to that characterizing the Schönlein-Henoch syndrome. He also had joint pains and developed severe abdominal colic with vomiting of blood. Surgical opinion was sought and it was decided to perform a laparotomy. When the small intestine was examined petechial haemorrhages were observed in the wall of the gut and also in its mesentery; no other abnormality was found. Albuminuria was present on the day of operation and continued from that time. The blood pressure rose steadily reaching 175/150 mm. Hg. He gradually became more drowsy, convulsions supervened, and he died in uraemia six weeks after the onset of the illness.

FIG. 7.—Kidney (H. and E. ×9) showing patchy infarction of cortex.

Post-mortem examination showed marked hypertrophy of the myocardium. The macroscopic appearances of the kidney were those of polyarteritis nodosa and, histologically, were interpreted as polyarteritis nodosa with acute hypertensive changes (Fig. 7).

This patient's earlier manifestations could be identified with those of the Schönlein-Henoch syndrome but the subsequent events indicated the development of polyarteritis nodosa with renal ischaemia and hypertension. This case supports the view that the Schönlein-Henoch syndrome and polyarteritis nodosa are closely related members of the family of collagen disease.

Summary

Thirty-nine cases of collagen disease in children are reported, 35 of these being typical of the Schönlein-Henoch syndrome. Four further cases are described in greater detail. The aetiology and prognosis are considered.

We wish to thank Professor N. B. Capon for his most helpful criticism and advice, Dr. Blair Macaulay for carrying out skin tests, Dr. E. G. Hall for pathological reports and some photographs, Mr. R. R. Green for other photographic work, and Dr. R. W. Brookfield and Dr. F. Pierce Hudson for permission to publish details of two of the atypical cases.

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THROMBOCYTOPENIC PURPURA FOLLOWING MEASLES

BY

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The occurrence of thrombocytopenic purpura as a complication of the acute infectious fevers is uncommon, and two such cases with unusual features which occurred after measles are reported.

Case Reports

Case 1. C.M., a girl aged 3 years and 7 months, had been in good health until February 6, 1951, when she became unwell with fever and catarrhal symptoms followed three days later by a typical measles eruption. The course of the illness was mild, but on February 17, haemorrhagic vesicles appeared on the tongue followed by bleeding from the gums. Two days later on admission to hospital the child appeared in good general health except for a generalized purpuric rash with ecchymoses of the limbs and petechiae of the buccal, palatal and conjunctival mucosae. Haemorrhagic vesicles were also present on the tonsils; the spleen was not palpable. Thrombocytopenia was present (14,500 platelets per c.mm.), with a bleeding time in excess of 10 minutes and poor clot retraction. The urine contained a few red blood cells. There was no family history of any bleeding tendency.

On February 27, a bone marrow aspiration was performed. The megakaryocytes were normal in number, their cytoplasm being, if anything, slightly more condensed than normal. Two further purpuric lesions of the lower lip appeared on February 28, but there was no subsequent purpura or bleeding.

The child remained well although marked thrombocytopenia persisted during the next four weeks (Table 1).

Penicillin, 250,000 units, was given intramuscularly twice a day from February 21 to March 4 because the throat was injected but no pathogenic organisms were cultured. During the following two months there was no further purpura, the platelet count and bleeding time remaining normal.

Case 2. J.P., a girl aged 5 years 10 months, was admitted to hospital on March 29, 1951. One week previously she had developed a mild attack of measles. On the day before admission generalized bruising of the skin and petechial haemorrhages appeared, accompanied by bleeding from the gums and buccal mucosa. The child had also complained of vague pains in the legs for the previous four or five days, associated with anorexia and lethargy. There was nothing relevant in the past or family history.

TABLE 1

RESULTS OF BLOOD EXAMINATION IN CASE 1

Date	R.B.C. (per c.mm.)	Hb. (%)	W.B.C. (per c.mm.)	Platelets (per c.mm.)	Bleeding Time (min.)
19.2.51	4,620,000	94	8,300	23,000	>10
21.2.51				17,200	
24.2.51	4,610,000			23,050	
26.2.51				18,400	
28.2.51				29,100	
2.3.51				42,300	
7.3.51				63,000	
10.3.51				40,800	
15.3.51				45,000	
5.4.51				484,000	
4.5.51	4,470,000			563,220	2½

Examination of cellular marrow obtained by iliac crest puncture gave:

Granulocytes	24%
Lymphocytes	42%
Normoblasts	34%

On examination the child was ill with a temperature of 100·4° and a pulse rate of 120 per minute. There were haemorrhagic vesicles on the tongue, a subconjunctival haemorrhage in the right eye and bleeding from the gums. There were multiple petechial haemorrhages in the skin of the trunk and several large fresh bruises on the legs. The spleen and liver were not enlarged but some small cervical glands were palpable. Frank haematuria and heavy albuminuria were present. Hess's capillary resistance test was

TABLE 2
RESULTS OF SERIAL BLOOD COUNTS IN CASE 2

Date	Hb. (%)	W.B.C. (per c.mm.)	Polymorphs (%)	Lymphocytes (%)	Monocytes (%)	Turck Cells (%)	Basophils (%)	Eosinophils (%)	Platelets (per c.mm.)	Bleeding Time (min.)	Reticulocytes (%)
30.3.51	67	4,000	64	31	5				12,000	>10	
	Blood transfusion: 1 pint of fresh blood										
2.4.51	50	2,000	8	70	18	4			11,000		
3.4.51	42	1,700	<1	94	2	4					
4.4.51			*Blood transfusion: 1 pint of fresh and 1 pint of stored blood*								
5.4.51	94	2,800	1	70	24	5					8
6.4.51	94	2,200	18	63	16	3			44,000		
9.4.51	100	5,000	48	46	6				20,000		
12.4.51	98	6,000	34	65		1			100,000		
23.4.51	84	9,000	37	54	4	1	1	3	230,000		
17.7.51	84	6,000	37	51	10		1	1	200,000		

Examination of cellular marrow obtained by iliac crest puncture gave:

Late normoblasts	59·5%
Intermediate normoblasts	22 %
Early normoblasts	2·5%
Lymphocytes	6·5%
Metamyelocytes	2·5%
Myelocytes	6·0%
Eosinophils	0·5%
Myeloblasts	0·5%

Blood groups: J.P. Group B Rh+; Mother Group B Rh+; Father Group B Rh+

The myeloid : erythroblastic ratio was 0·2 : 1. Megakaryocytes were present in the usual numbers and showed no morphological changes. There was normoblastic hyperplasia and maturation arrest of polymorphs.

positive. The blood picture and serial blood counts are shown in Table 2.

On the day after admission the child's condition had deteriorated and she was still bleeding from the buccal mucosa and urinary tract. Blood taken for culture was sterile after four days. A diagnosis of thrombocytopenic purpura was made and a pint of fresh maternal blood was transfused. A course of systemic penicillin, 300,000 units daily intramuscularly, was begun on the same day. During the subsequent four days her general condition remained unchanged but oozing from the buccal mucosa and haematuria persisted. There was also considerable bleeding and haematoma formation at the site of transfusion. Daily blood counts showed a steady fall in the haemoglobin level with a marked leucopenia and the development of almost complete agranulocytosis on April 3. For this reason a second transfusion with one pint of paternal blood and one pint of stored blood was given on April 4 with rapid improvement; all bleeding ceased and the blood picture returned to normal during the next few days. Penicillin treatment was stopped on April 11; no other treatment was given. The child was discharged on April 13, and during the following three months she remained well with no recurrence of bleeding.

Comment

Purpura may present during the course of the acute infectious fevers in three forms. First, it may be confined to the rash where it is probably an exaggeration of the mechanism causing the exanthem. Secondly, it may occur in the haemorrhagic type of these infections when it appears early and is associated with a severe illness which may prove fatal. This is probably due to septicaemia, often streptococcal, rather than to toxaemia from the primary infection. Thirdly, purpura may occur during the period of convalescence from scarlet fever (Box, 1933), rubella (Ackroyd, 1949) and measles (Miller, 1941).

In his review of such cases Miller stated that the measles was usually mild and that purpura occurred during the second week. In the cases described

by Corbia (1927), Sarrouy (1934), Perlman (1934) and Miller (1941) there was a marked thrombocytopenia during the purpuric phase with a gradual return of the platelets to normal numbers. In that reported by Laurent (1933) there was no decrease of platelets. No bone marrow examinations were recorded.

It is the association of purpura with a preceding infectious fever that is of interest and may pass unrecognized: in Case 1 prolonged thrombocytopenia was present without further haemorrhagic manifestations after the initial phase. In Case 2 the anaemia resulting from severe bleeding from various sites required transfusion on two occasions. The development of an agranulocytosis during the course of the illness has not previously been described.

In both cases the bone marrow was examined during the acute phase of the illness, and normal megakaryocyte formation was present. In Case 2, there was a maturation arrest of the polymorphs.

The mechanism of thrombocytopenia occurring in such cases is obscure, although Ackroyd suggests that it is the result of an allergic response in a susceptible individual.

Summary

Two cases of thrombocytopenic purpura following mild attacks of measles are described. One patient developed agranulocytosis during the acute haemorrhagic phase.

Bone marrow examination in both instances demonstrated the presence of normal megakaryocytes.

Attention is drawn to the association of thrombocytopenic purpura and the acute infectious fevers.

We wish to thank Dr. G. H. Newns and Dr. J. W. Todd for permission to publish these cases.

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MYCOTIC ANEURYSM OF THE ABDOMINAL AORTA

BY

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Mycotic aneurysms occurring during the course of bacterial endocarditis have hitherto been largely of academic interest owing to the fatal nature of the primary condition, but with recent advances in the treatment of endocarditis such complications are becoming of greater importance, particularly as they may themselves be a cause of death. Haemorrhage from rupture of a mycotic aneurysm was the main cause of death in 17 of the 408 cases of subacute bacterial endocarditis treated with penicillin in the Medical Research Council series (Cates and Christie, 1951), and in two cases a peripheral aneurysm developed after the end of treatment.

Mycotic aneurysms seldom develop in the abdominal aorta and there are few reports of such a complication of bacterial endocarditis. We recently observed the following case of pneumococcal endocarditis in a child, whose death was caused by rupture of a mycotic aneurysm of the abdominal aorta.

Case Report

A girl of 10 years and 11 months was admitted to the Royal Hospital for Sick Children, Edinburgh, on May 4, 1951.

The child was well until three weeks before admission when she came home from school feeling cold and shivery. That evening she became flushed and feverish and was in bed for two days, after which she felt better. However, the symptoms recurred within a day of getting up and she had to return to bed. From that time until admission she was listless and ill, with intermittent fever and occasional vomiting. Constipation was troublesome. She did not complain of pain and had no cough. She was treated with a sulphonamide drug without much effect. A few days before admission she had an epistaxis lasting about 10 minutes.

She was born at full term by spontaneous delivery after a normal pregnancy, and her early development was satisfactory. Past illnesses included measles at 2 years, pertussis at 5 years, and varicella at 7 years. She had several attacks of bronchitis between 1 and 5 years but none thereafter.

The family doctor stated that she had never had a heart murmur previously and had no history of rheumatism.

Her parents were healthy and she had two sisters, aged 7 and 12 years, who were both well. There was no family history of rheumatism. Social conditions were good.

On admission she was seen to be a well developed and well nourished girl, rather flushed. The temperature was 100°, pulse rate 150 per minute and respiration rate 32 per minute. The skin was healthy with no rash or petechiae. There was no clubbing of the fingers.

The pulse was regular in time and force: blood pressure 125/65. The apex beat was palpable in the fifth left interspace just outside the midclavicular line. A loud systolic murmur was heard, maximal at the apex but audible over the whole praecordium.

The tongue was dry and furred. There was no abdominal tenderness or rigidity and no abnormal mass was palpable. The spleen could not be felt. There were no enlarged lymph nodes.

No abnormality was found in the respiratory or nervous systems. The optic fundi were normal and remained so throughout her illness.

Investigations. A blood count gave Hb. 13·7g.%, leucocytes 16,400 per c.mm. (polymorphs 84%, lymphocytes 14%, monocytes 2%). The blood sedimentation rate was 22 mm. in one hour (modified Cutler micromethod). The urine had a specific gravity of 1020. No albumin or sugar was found, but a few red and white cells were seen microscopically.

The Mantoux test (1/1000) was negative, as also was the Paul Bunnell test. There was no agglutination with *B. typhosus*, *B. paratyphosus* A and B, *Salmonella*, or *Brucella abortus*.

Progress. On the day after admission her temperature rose to 104°; it fell next morning and rose again to 101·4° on the following day. Blood was taken for culture on two occasions when the temperature was rising, and both specimens grew a pneumococcus, of the same sensitivity to penicillin as the standard Oxford staphylococcus.

A tentative diagnosis of bacterial endocarditis was made and treatment with penicillin, 500,000 units intramuscularly every four hours, was started on the third day after admission. On the fourth day she suddenly developed complete hemiplegia on the left side and had signs of slight meningeal irritation. A lumbar puncture showed clear cerebrospinal fluid, with 49 cells per c.mm., mainly lymphocytes, and protein 30 mg.%, sugar 55 mg.% and chlorides 700 mg.%. A search was made for further embolic signs and a small, acutely tender, purple swelling was found in the pulp of the right fifth finger.

An electrocardiogram taken five days after admission showed a rate of 115/minute, a normal rhythm, no axis deviation and PR interval 0·14 seconds. The unipolar extremity leads and precordial leads were normal.

One week after admission she complained of pain in the left hypochondrium and tenderness was elicited on deep palpation in that region, but the spleen could not be felt. During the next few days, her temperature gradually fell and the hemiplegia improved. No change was noted in the heart murmur and no more embolic signs were found. In view of this improvement, no further lumbar puncture was carried out.

Her general condition remained good and she became much brighter. However, three weeks after admission her temperature rose to 102° F. and she complained of pain in the left shoulder. A radiograph of the chest taken in the ward showed no pulmonary lesion and no enlargement of the heart. The white blood cell count was 17,200 per c.mm., and further blood specimens were sterile on culture.

Thereafter she again improved and her temperature fell to normal for nine days, during which she was rather apathetic, although her general condition was remarkably good. She occasionally complained of pain in the limbs, especially in the left hip, abduction of which was painful. No abnormality of this joint was visible radiologically.

At the end of the apyrexial period the following results were obtained: Hb. 13·7 g.%; leucocytes 16,600 per c.mm. A chest radiograph showed no pulmonary lesion, and an electrocardiogram was normal. Blood pressure was 140/100. The urine was normal, with 11 mg.% blood urea nitrogen. Serum albumin was 4·95 g.% and serum globulin 3·7 g.%.

Five weeks after admission, her temperature again rose and she lost her appetite. Next day she complained of mid-abdominal pain: no abnormality was found on examination of the abdomen. The pain continued however, and two days later a firm, tender, pulsatile swelling was just palpable below the umbilicus. This swelling increased slowly in size and a systolic bruit transmitted down the femoral arteries was audible. A tentative diagnosis of aneurysm of the abdominal aorta was made and streptomycin was started in addition to the penicillin. It was decided that laparotomy, with surgical treatment of the aneurysm if possible, offered the only hope of recovery, but before this could be carried out she suddenly complained of severe abdominal pain and a swelling appeared in the left side of her abdomen. Blood transfusion was immediately started, but she rapidly became extremely pale and weak and died within half an hour.

Necropsy Report

Necropsy was carried out on June 13, 1951. The body was that of a well developed female child aged 11 years. No congenital abnormality was found on external examination.

Head. The dura mater and leptomeninges were healthy. The brain was firm, but on section there was a large area of softening in the right cerebral hemisphere which had partially destroyed the basal ganglia and the wall of the right lateral ventricle (Fig. 1). The softened area measured 6 cm. by 3 cm. by 2 cm. and showed pronounced yellow discoloration. The appearance was that of a large infarct resulting from embolism of the right middle cerebral artery or one of its large branches. Dissection of the right middle cerebral artery and of its major branches failed to demonstrate an aneurysm. The left cerebral hemisphere was normal. The mid-brain, pons, cerebellum and medulla oblongata were healthy.

Thorax. The pharynx and oesophagus, trachea, bronchi and lungs were healthy. The pericardium was clear and glistening. There was no free fluid in the pericardial sac. The heart was moderately enlarged, chiefly as a result of dilatation of the right ventricle. The myocardium of the right ventricle was flabby. The right atrium was normal and the tricuspid valve admitted three fingers. The pulmonary valve was healthy. The myocardium of the left ventricle was of normal thickness and rather pale. The aortic valve was healthy. The mitral valve showed an area of ulceration 0·5 cm. in diameter extending upwards from the valve ring. There were two groups of pale vegetations over the posterior cusp. The endocardium of the left atrium was healthy. The coronary arteries and great vessels had a normal appearance.

Abdomen. A very large quantity of clotted blood was lying extraperitoneally in the anterior and lateral abdominal walls. The peritoneum was clear and glistening with no free fluid in the peritoneal sac. The stomach and intestines were healthy. The liver was slightly enlarged and the cut surface was pale. The spleen was twice the normal size. The capsule was thickened over the lower pole and a large infarct, 4·5 cm. by 2 cm. by 1·5 cm., was present in this situation (Fig. 2). The infarct was clearly demarcated from the surrounding splenic pulp and was bright yellow. The splenic pulp was pale and soft. The pancreas and suprarenal glands were healthy. The left kidney was

FIG. 1.—S

FIG. 3.—
posterio

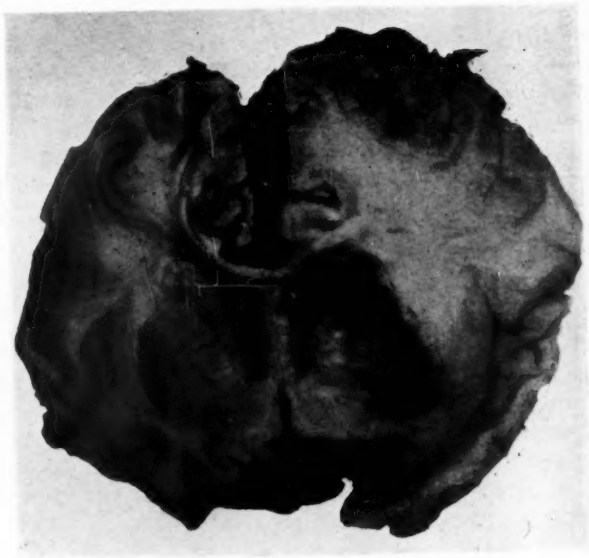

FIG. 1.—Section of brain showing destruction in the right cerebral hemisphere.

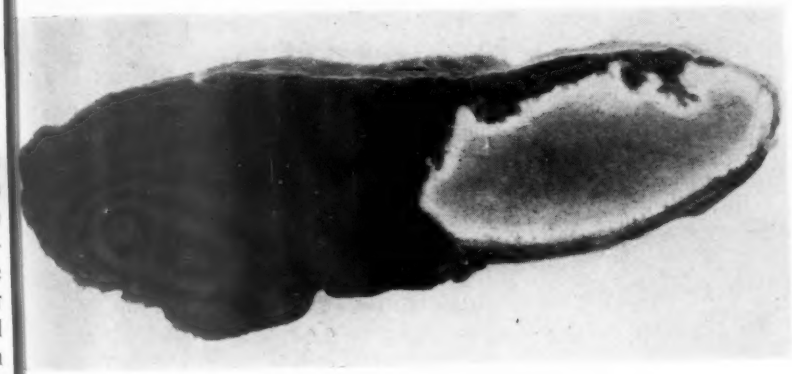

FIG. 2.—Section of spleen showing infarct.

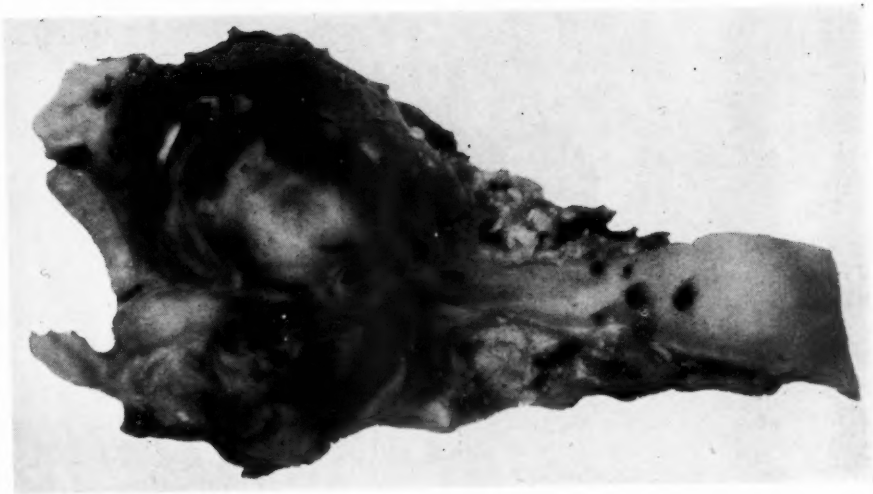

FIG. 3.—Abdominal aorta opened posteriorly to display the aneurysm.

surrounded by a mass of retroperitoneal blood clot. Both kidneys were structurally normal. The ureters, bladder, ovaries and uterus were healthy.

The abdominal aorta was then examined and a large aneurysmal dilatation, 7·5 cm. by 4 cm. by 4 cm., was found arising from the posterior aspect of the aorta 1·5 cm. above the bifurcation. The wall of the aneurysm was composed largely of fibrin and laminated blood clot. Only a narrow central band of aortic wall remained (Fig. 3). The dilatation was thus a false sac which had been formed by slow leakage from a mycotic aneurysm of the lower abdominal aorta and had eventually ruptured, causing a fatal retroperitoneal haemorrhage. A mural thrombus was also present in the left common iliac artery and the left external iliac artery was completely occluded by thrombus. The right common iliac artery and its branches were clear.

Bacteriological Report. A direct film made from one of the vegetations on the mitral valve showed a few polymorphonuclear leucocytes, lymphocytes and Gram-positive cocci. Only post-mortem contaminants were obtained on culture. The brain lesion was sterile.

Histological Report. The myocardium was healthy and the interstitial tissue had a normal appearance. There was no evidence of previous rheumatism. The vegetations from the mitral valve were found to consist of organizing platelet thrombi with infiltration of the valve cusp by polymorphonuclear leucocytes and lymphocytes. No organisms were found. The valvular endothelium had been destroyed and the appearance was that of healing ulcerative endocarditis.

Sections from the wall of the aneurysm in the aorta confirmed that it was composed of fibrin clot. Masses of polymorphonuclear leucocytes were enmeshed in the fibrin network.

A large infarct with a well defined margin was present in the spleen. The infarcted area showed complete loss of structure. The surrounding pulp contained numerous polymorphonuclear leucocytes. The Malpighian bodies appeared normal.

The infarcted area of the brain showed complete loss of nerve cells and ground substance. At the margin of the infarct a reparative gliosis was taking place.

The liver, kidneys and pancreas showed no abnormality.

The findings may be summarized as acute endocarditis, aneurysm of the abdominal aorta, infarction of brain and spleen, terminal retroperitoneal haemorrhage.

Discussion

Bacterial infection may invade a vessel wall from without or from within, so that mycotic aneurysms may be of extravascular or intravascular origin. Bacterial endocarditis is much the most common cause of the latter group, having been present in 187 of 217 collected cases of mycotic aneurysm of intravascular origin (Stengel and Wolferth, 1923).

Subacute bacterial endocarditis is not common in children and malignant endocarditis is equally rare. Schlesinger (1928) found only 10 cases of acute malignant endocarditis in 67 years in the records of The Hospital for Sick Children, Great Ormond Street. Pneumococcal endocarditis is particularly unusual in childhood as it occurs in an older age group than endocarditis due to other organisms. Thayer (1931) found that only 4·76% of his 306 cases occurred in the first two decades. The disease usually has a rapidly fatal course, although Blumer (1923) reported 16 patients who survived for more than three months.

The portal of entry of the pneumococcus is usually known (Thayer, 1931) but in the present case no primary focus of infection could be discovered. In one-third of a series of 23 cases, however, Lord (1932) was uncertain of the source of the infection. The pneumococcus usually attacks a healthy valve, as in this case, and in the majority of instances the lesions are confined to the left side of the heart.

Although aneurysms of the heart valves and root of the aorta due to direct ulceration are relatively common, mycotic aneurysms of embolic origin occur infrequently. Thayer (1926) found no embolic aneurysms in 60 necropsies on cases of bacterial endocarditis and Blumer (1923) found only nine in 150 collected necropsies, two of these being in the aorta.

Aneurysm of the Abdominal Aorta. Saccular aneurysms of the abdominal aorta are not uncommon in adults but are seldom encountered in children. Only three of Nixon's 233 patients were under 20 years of age (Nixon, 1911). These aneurysms are usually caused by syphilis or arteriosclerosis (Epstein, 1945) and bacterial infection is rare, but it assumes greater relative importance in childhood when syphilis and arteriosclerosis are infrequent (Bronson and Sutherland, 1918). Kampmeier (1936) collected 381 cases of aneurysm of the abdominal aorta but did not mention bacterial infection in discussing the aetiology. In a series of 96 cases of abdominal aneurysm, Scott (1944) found that in 68 the aorta was involved. Eighteen of his whole series were cases of mycotic aneurysm but in only three of

these was the aorta involved. Thirteen of the 18 patients had bacterial endocarditis but it was not stated whether these included the three cases of aortic aneurysm. Stengel and Wolferth (1923) found 66 cases of mycotic aortic aneurysm, but in 60 of these the root or arch of the aorta was involved and it was not stated whether any of the remaining six were abdominal.

No mycotic aneurysms were found by Hubeny and Pollack (1940) in 48 cases of saccular aneurysm of the abdominal aorta, nor by Garland (1932) in 16 cases. Rottino (1943) reported that four of his 31 cases were mycotic but none was due to endocarditis. In the series of 596 cases of aneurysm reviewed by Mills and Horton (1938) in 26 the abdominal aorta was involved, but none was due to endocarditis.

Mycotic aneurysms of the abdominal aorta may be caused by weakening of the vessel wall by contiguous disease as in Preioni's case referred to by Revell (1945), which was due to a pneumococcal abscess, but those arising in the course of bacterial endocarditis are considered to be due to small infected emboli from the valves which lodge in the vasa vasorum of the aortic wall (Eppinger, 1887; Chamberlain, 1943). A similar pathogenesis may be invoked for primary mycotic aneurysms, such as those described by Revell (1945), which occur during the course of pyogenic infection elsewhere in the body. These are presumably due to bacterial embolism of the vasa vasorum, as it is unlikely that bacteria could cause endarteritis of the intact intima of the abdominal aorta.

Rarely, tuberculosis may be the cause, either by spread of the tuberculous process to the aortic wall from neighbouring lymph nodes (Dafoe, 1925) or possibly by bacterial embolism as in the case described by Jacobi (1890), in which a girl of 5 with a tuberculous hip developed an aneurysm of the abdominal aorta.

It is possible that congenital deficiency of elastic tissue in the aortic wall could result in an aneurysm, and Gibson (1946) reported such a case in a boy of 16 months, who died after rupture of an aneurysm of the abdominal aorta for which no cause was found. However, the congenital nature of the lesion was not proved and it could equally well have been a primary mycotic aneurysm.

A search of the literature has revealed only five reported cases of mycotic aneurysm of the abdominal aorta caused by bacterial endocarditis. All occurred in childhood.

CASE 1 (AITKEN, 1898). A boy of 9 years, with a past history of rheumatism, who died of heart disease. Necropsy revealed vegetations on the aortic valve, with perforation of one of the cusps. There was an aneurysm the size of a golf ball on the anterior aspect of the abdominal aorta at its bifurcation.

CASE 2 (ALEXEJEW, 1898). A girl of 10 years, who had pain and depression for eight weeks. There was palpable pulsation under the umbilicus, and the pulse in the left crural artery was smaller than that on the right. Necropsy revealed vegetations on the mitral valve and an aneurysm of the abdominal aorta.

CASE 3 (BAGINSKY, 1908). A boy of 7 years and 9 months, with no history of rheumatism, was admitted with pain in the extremities. He developed a pulsating mass in the mid-abdomen, and necropsy revealed a large aneurysm of the abdominal aorta, and another the size of a walnut on the subclavian artery. There were vegetations on the mitral valve and infarcts in the spleen and kidney.

CASE 4 (NIXON, 1911). A boy of 14 years died of infective endocarditis, and had an aneurysm the size of a pigeon's egg on the abdominal aorta at the bifurcation.

CASE 5 (ROST AND FISCHER, 1928). A child of 11½ years, who had subacute bacterial endocarditis, developed an aneurysm of the abdominal aorta. No necropsy was allowed.

The first four cases can be accepted, but in the case of Rost and Fischer the diagnosis was not verified by post-mortem examination, and therefore the aneurysm may have been on a smaller vessel such as the superior mesenteric artery, a commoner site than the abdominal aorta. The three cases reported by Scott (1944) have not been included because no clinical details were given, and it was not stated that they were due to bacterial endocarditis.

With an increasing proportion of recoveries from bacterial endocarditis, such cases may be encountered more frequently, as no doubt many cases in the past have been missed, or considered of no importance because of the serious nature of the primary illness, and therefore not reported. Since the behaviour of mycotic aneurysms under medical treatment is unpredictable (Cates and Christie, 1951), it is important that a careful watch should be kept for such complications, which may have to be dealt with surgically, especially when they are so situated as to endanger the patient's life.

Summary

Mycotic aneurysm of the abdominal aorta is an uncommon but serious complication of bacterial endocarditis.

The case of a child who died after rupture of such an aneurysm is reported, with details of the necropsy.

Five further cases, all occurring in childhood, have been collected from the literature.

The condition is briefly reviewed.

We are grateful to Dr. D. N. Nicholson for permission to report this case.

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A CASE OF KAPOSI'S HAEMANGIOSARCOMA

BY

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In 1872 Kaposi described a dermatological condition which he called 'idiopathic multiple pigment sarcoma'. At the present time it is often known as Kaposi's haemangiosarcoma. Kaposi described it as affecting the skin, and it certainly affects this part most often, but for years it has been known to involve other organs. In 1940, Choisser and Ramsey reviewed the literature and mentioned a total of 600 cases since 1872. Stats (1946) lists the sites which, after the skin, may be affected most often. He mentions the glans penis, the submucosa of the gastro-intestinal tract, the respiratory tract and the lymph nodes. Less common sites are the spleen, liver, heart, diaphragm and bladder. Seagrave (1948) has described a case in which the submucosa of the gastro-intestinal tract and the skin were involved. In such cases blood is often found in the stools. The disease is said to be rare in negroes, but Kaminer and Murray (1950) record 38 cases in the South African Bantu occurring in the period 1942-49. It is certainly very uncommon in children and appears to occur mostly in adults over the age of 40. MacKee and Cipollaro (1936) mention an incidence of less than 1% under the age of 10 years.

The sex incidence is predominantly male. Denzer and Leopold (1936) recorded the clinical aspects of the disease in a male child of 4½ years; the necropsy findings were subsequently described by Stats (1946). The case recorded here is that of a boy, and it illustrates the very uncommon form of the disease without skin manifestations. Choisser and Ramsey (1940) described two cases of Kaposi's tumour of the heart without skin lesions; in these cases the right auricle was involved. Cardiac nodules have also been described in cases with cutaneous involvement. Tedeschi, Folsom and Carnicelli (1947) mention three cases affecting viscera without skin manifestations. These authors consider the disease to be systemic in nature affecting various parts at the same time. Aegerter and Peale (1942) consider the condition to be a vascular cancer and regard the visceral lesions as true metastases. However, lymph node involvement is often not regional to any affected organ, and supports the view that the disease is a systemic affection like a reticulo-endotheliosis, although the disease is generally considered to be neoplastic.

The case recorded here illustrates this point.

Case Report

A Bantu male child aged 6 years was admitted to the Baragwanath Hospital in July, 1950. He had developed a sore throat and swelling of the neck a week before. There were no other symptoms, and his previous history was satisfactory.

The parents were healthy and three siblings were all apparently well.

The patient was a fairly well nourished child lying comfortably in bed. He did not appear ill or distressed. The temperature was 97·4°, the pulse 78 per minute, and respiration 26 per minute.

Careful examination of the entire skin and the genitalia revealed nothing abnormal. There was no oedema of the extremities. (Swelling of the extremities has been noted by various authors as the first sign of this disease.) The tongue and mucosa of the mouth were normal. The tonsils were slightly congested but not enlarged.

Nothing abnormal was detected in the clinical examination of the cardiovascular or respiratory systems. The blood pressure was 100/65.

The central nervous system was normal. Examination of the abdomen revealed a palpable liver one finger breadth below the costal margin. It was firm, regular and not tender. The spleen was palpable two finger breadths below the costal margin. It was firm but not tender.

The lymph nodes of the occipital, cervical, submental, right axillary and both inguinal regions were all palpably enlarged. The largest was about 3 cm. by 2 cm. They were discrete, felt distinctly rubbery, were freely mobile, and were not tender.

Investigations. The Mantoux test was negative up to 1/10.

A full blood count on admission gave: Hb. 14·9 g.%, leucocytes 9,800 per c.mm. (neutrophils 47%, monocytes 9%, lymphocytes 39%, eosinophils 5%), packed cell volume 44%, sedimentation rate 23 mm. per hour. The corrected sedimentation rate was slightly increased. Malaria parasites were not observed. A subsequent blood count, five weeks later, gave: Hb. 12·6 g.%, leucocytes 8,800 (neutrophils 42%, monocytes 3·5%, lymphocytes 46·5%, eosinophils 7·5%, basophils 0·5%).

The standard Eagle test and the modified Ide test were both negative.

The Paul-Bunnell test was negative.

The benzidine test for occult blood in the stool was negative.

Radiographs of the chest showed no abnormality and no evidence of mediastinal glandular enlargement. The heart was normal in size and shape.

The urine had a specific gravity of 1020. Tests for albumin were negative.

An electrocardiogram was normal.

A sternal marrow puncture gave the following results: blast cells 0·5%; myelocytes (neutrophil 2%, eosinophil 1%) 3%; metamyelocytes (neutrophil 3%, eosinophil 1·5%) 4·5%; staff cells 4%; polymorphonuclears (neutrophil 9%, eosinophil 9%) 18%; monocytes 1%; lymphocytes 23%; erythroblasts 3%; normoblasts 41%; plasma cells 1%; reticulum cells 1%; total nucleated cell count 42,400 per c.mm.; megakaryocytes 11 per c.mm. Myeloid: erythroid ratio 0·7 : 1; myeloid: lymphoid ratio 1·3 : 1.

The bone marrow was of normal cellularity with slightly increased reactions in the lymphoid and erythroid series. This was borne out by the reduced myeloid : lymphoid and the reversed myeloid : erythroid ratios.

A special feature was the increase in eosinophils in all stages of maturation.

A skin biopsy taken from the anterior abdominal wall did not reveal any abnormality on histological examination.

A needle liver biopsy showed no pathological lesion.

An inguinal lymph node biopsy showed, on histological examination, loss of the normal architecture and its replacement by a fibro-sarcomatous type of tumour with numerous blood spaces in which mitotic figures were plentiful. The histological features were strongly suggestive of Kaposi's haemangiosarcoma (Dr. J. Higginson).

An enlarged axillary lymph node was subsequently removed and its microscopical examination confirmed the presence of a similar lesion to that found in the inguinal gland. Here the report indicated the presence of a haemorrhagic sarcoma with numerous blood vessels and moderate activity (Figs. 1 and 2). Some plasma cell infiltration was also noted.

Progress and Treatment. The diagnosis of a haemangiosarcoma of the Kaposi type was established. It was decided, before instituting general treatment, to apply x-ray therapy to a single enlarged lymph node and assess the effect of the treatment by its subsequent removal and examination. Therefore, a single dose of 1000 r of medium voltage x-ray therapy (135 K.V.) was applied to an enlarged submental gland of about 2 cm. in diameter. This gland became smaller, and four weeks after the treatment it was removed and examined, disclosing the presence of interstitial fibrosis which indicated a definite response to the therapy (Figs. 3 and 4).

Four weeks after the biopsy, the child was given general x-ray therapy as follows:

Left groin	..	total dose of 1500 r (180 K.V.)
Right groin	..	total dose of 1000 r
Right lateral neck		total dose of 1200 r
Left lateral neck		total dose of 1200 r
Right axilla	..	total dose of 2000 r
Spleen	.. ..	total dose of 1500 r

This treatment was applied for seven weeks, and after it was completed the liver and spleen were no longer palpable, and only small, shotty glands could be felt in the groin, axilla and neck.

Discussion

The presenting features in this child were generalized lymphadenopathy and hepatosplenomegaly. Various diagnostic possibilities, such as tuberculosis, syphilis, glandular fever, leukaemia, were excluded by appropriate investigations. The final diagnosis of Kaposi's haemangiosarcoma could only be made by lymph node biopsy and histological examination. This was confirmed by the presence of the same lesion in another gland taken from a different region. This case appeared to be remarkable because it showed none of the cutaneous lesions which commonly occur in this disease.

The patient had an eosinophilia, which has been found in other cases. Dörffel (1932) mentions secondary anaemia as a common feature but this was not present. The sternal marrow puncture specimens showed an increase in the eosinophils in all stages of maturation. There was normal cellularity with slightly increased reactions of the lymphoid and erythroid series. Stats found an active bone marrow with a normal cellularity in two cases. In this case the spleen was enlarged and the palpable enlargement disappeared after x-ray therapy. We might assume that the disease was present in this organ, although there was no absolute proof. Symmers (1941) reported a case in which the spleen, weighing 1,000 g., was filled with the Kaposi's lesion. But in other cases of splenomegaly in this disease, the haemangiomatous deposits were not present; Dalla Favera (1911) records such a case.

The needle liver biopsy did not reveal any abnormal histology, but this need not preclude the presence of the disease in this organ.

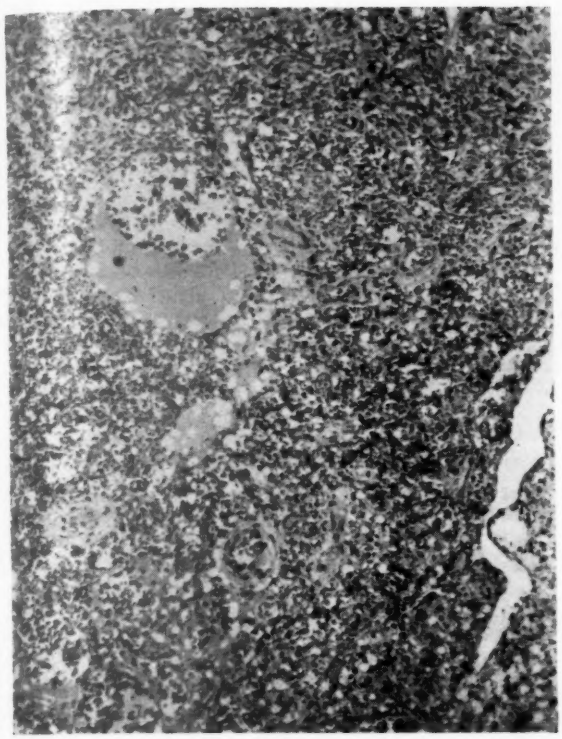

FIG. 1.

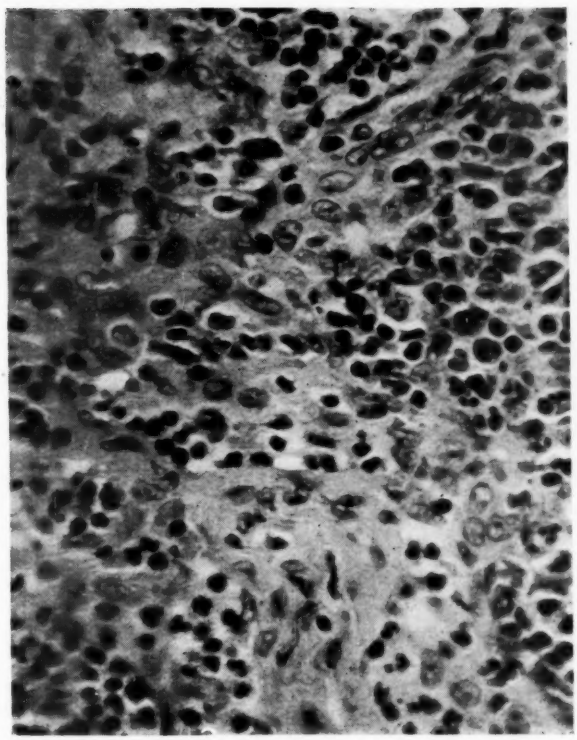

FIG. 2.

FIGS. 1 and 2.—Kaposi's tumour before treatment (low power). High power view of Fig. 1.

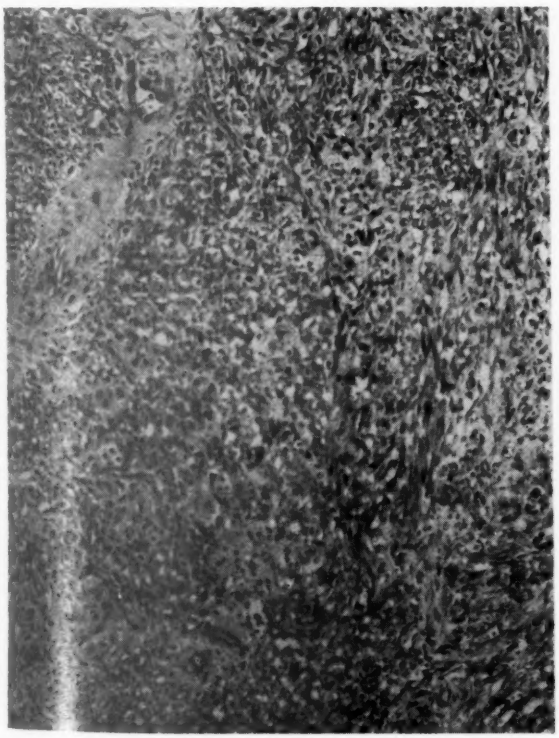

FIG. 3.

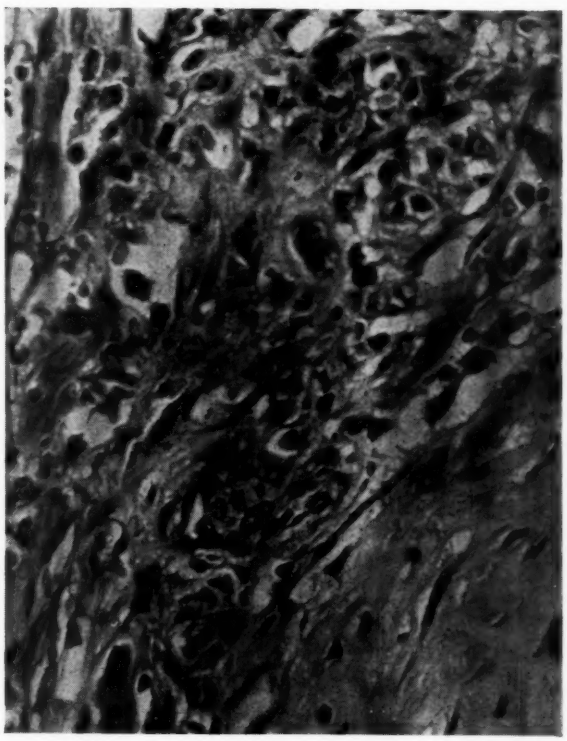

FIG. 4.

FIGS. 3 and 4.—Low power view of lymph node of Kaposi's tumour after x-ray therapy showing a definite response by the presence of interstitial fibrosis. High power view of Fig. 3.

Clinical, electrocardiographic and radiological examination of the heart did not reveal any abnormality, but, here again, one cannot exclude the presence of lesions in the heart. Occult blood is often found in the stools of patients with gastro-intestinal involvement, but this patient had no such abnormality. A skin biopsy showed no abnormality and there was no clinical evidence of any skin lesions.

In this case most of the superficial lymph nodes were enlarged, but there was no radiological evidence of mediastinal glandular involvement or clinical evidence of abdominal glandular enlargement. We have only evidence of generalized superficial lymph node involvement and possible splenic affection, and this might be in favour of relating this disease to the reticulo-endothelioses. X-ray therapy given to the affected glands and the spleen led to a great diminution in their size.

Summary

A case is presented of Kaposi's haemangio-sarcoma occurring in a South African Bantu boy of 6 years. The superficial lymph nodes and spleen were affected without cutaneous involvement. The diagnosis was made by lymph node biopsy and histological examination. A single lymph node was first treated with x-rays, and the effect on the disease process assessed by its subsequent removal and microscopical examination. General x-ray treatment was applied, and the enlarged lymph nodes and spleen gradually became impalpable. The literature is briefly reviewed.

I should like to thank Dr. J. D. Allen, Medical Superintendent, Baragwanath Hospital, for permission to publish this case. I am also indebted to Dr. S. C. Heymann, Head of the Paediatric Department, University of the Witwatersrand, for his helpful criticism; to Drs. M. P. Shapiro and L. Cohen, Radiotherapy Department, Johannesburg Hospital, for their helpful advice and for allowing me access to their therapy notes; to Dr. J. Higginson for histopathological reports; to Dr. H. Hirsch for laboratory investigations; and to Drs. M. Shnier, P. Marchand, M. Goldberg and D. Warnes for providing biopsy specimens.

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ADDENDUM

This patient has been followed up at regular intervals for a year after the completion of x-ray therapy, and has remained completely free of any recurrence of the disease. He has no palpable lymph nodes and his spleen cannot be felt. Details of the x-ray treatment given to this patient was as follows:—

Left groin	total dose of 1500r in 5 daily fractions
Right groin	total dose of 1000r in 2 daily fractions
Right lateral neck	total dose of 1200r in 6 daily fractions
Left lateral neck	total dose of 1200r in 6 daily fractions
Right axilla	total dose of 2000r in 10 daily fractions
Spleen	total dose of 1500r in 10 daily fractions

The submental gland was treated with one dose of 1000r.

BACTERIAL ENDOCARDITIS AFTER A TAUSSIG-BLALOCK OPERATION IN A CASE OF UNUSUAL PATHOLOGY

BY

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(RECEIVED FOR PUBLICATION SEPTEMBER 19, 1951)

The introduction of the Taussig-Blalock operation to improve the pulmonary circulation in certain cases of cyanotic congenital heart disease has meant that successfully treated subjects, though much improved in their functional ability, have been given yet another cardiovascular abnormality. This extra lesion is an artificial ductus arteriosus, a condition which, when solitary and uncomplicated, is regarded as an indication for operative closure. One of the reasons for such closure is the risk to the patient of bacterial endocarditis developing. As quite a large series of successfully completed Taussig-Blalock operations have now been recorded it is rather surprising to find only one case (Hurst, Gleason and Schemm, 1949) reported in which bacterial endocarditis followed the operation, though this may in part be due to the fact that the commonest age incidence of this disease lies between 20 and 40 years.

The child to be described suffered such a complication and, in addition, had an unusual form of congenital heart disease.

Case Report

M.P. was first seen in December, 1947, when 5 years old. She was the seventh of eight living children, all the others being healthy. Two siblings had died of irrelevant causes. She was born at term, the product of a normal pregnancy and labour (though her mother had had some teeth extracted when 4 months pregnant) and weighed 8½ lb. at birth. She was bottle-fed from the neonatal period and had been subject to cough since she was 3 weeks old. Cyanosis was first noticed by the mother at 3 months. The baby had had a number of severe cyanotic attacks with dyspnoea and had been admitted to hospital in several of these attacks. In one of them, the last to occur, when aged 3 years, she had become unconscious and lost the use of the left arm for three weeks, presumably due to cerebral thrombosis. Her development was slow and she did not sit up alone until she was 2 years old, while she did not talk until 4 years of age and could not walk when examined. Solid food was taken from 9 months of age and her appetite was good. She recognized pictures but could only scribble illegibly and was regarded as mentally defective. There had been no convulsions. She was dyspnoeic on the slightest exertion.

On examination she was seen to be very small and weighed 28 lb. She was markedly cyanosed and had pronounced clubbing of fingers and toes. The limbs were thin and hypotonic and she was unable to stand. The chest wall bulged to the right of the sternum and the apex beat was not located. The heart sounds were loudest to the right of the sternum. There was a rough systolic murmur maximal in the third interspace close to the sternum and equally heard on both sides of this structure. The second sound was single. The blood pressure was 105/75. The lungs were clear and there was no sign of congestive failure. She had left otitis media.

Investigations showed Hb. 120%, and red cells 6,900,000 per c.mm.

Cardioscopy showed a boot-shaped heart, slight cardiac enlargement, apparently involving the right ventricle, or absent pulmonary cone, and a right-sided aortic arch. The lung fields were translucent.

An E.C.G. showed left axis deviation. There were prominent P waves in leads I and II, an inverted T_1 and slight elevation of ST_2 and ST_3 (Fig. 1).

An angiocardiogram showed that the aorta filled simultaneously with a narrowed pulmonary artery, and confirmed the right aortic arch. The ventricular septum was not defined.

The cardiographic findings cast serious doubt on the diagnosis of the tetralogy of Fallot which was entertained on the clinical and radiological findings. Brown states that such a finding in the absence of bundle branch block excludes a pulmonary stenosis, although Gasul, Richmond and Krakower (1949) recorded a case of the tetralogy with a patent foramen ovale (' pentalogy ') with left axis deviation, and two cases of the tetralogy with associated patent ductus arteriosus showed left axis deviation with unipolar leads (Sokolow and Edgar, 1950). The usual cause of left axis deviation is tricuspid atresia, but a persistent truncus arteriosus or a common

ventricle with hypoplastic right ventricle is sometimes found (Brown, 1950).

Under observation the child was seen to be severely incapacitated though she was taught to walk a little with support and slight exertion produced dyspnoea. She showed herself capable of learning and her speech and intelligence improved. In view of the miserable existence she was leading operation was advised, as the translucent lung fields led to the hope that a pulmonosystemic anastomosis would increase arterial oxygenation.

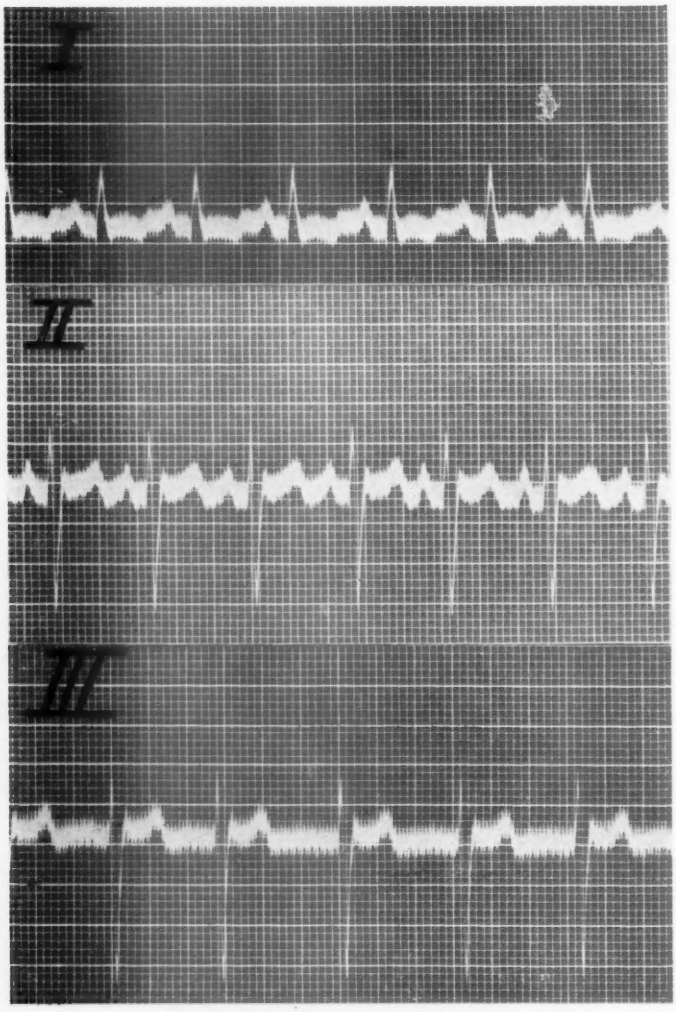


FIG. 1.—E.C.G. showing left axis deviation.

Operation was performed on August 11, 1948, under a general anaesthetic given by Dr. J. F. Rickards. The left third intercostal space was opened anteriorly with division of the second costal cartilage. A pulmonary artery of adequate size was present, and an end-to-side subclavian to pulmonary artery anastomosis was made using Blalock's early technique. On releasing the clamps, no leak occurred, the anastomosis appeared to function adequately, and the chest was then closed without drainage. The child's condition throughout the operation and her subsequent recovery were entirely satisfactory.

Progress after operation was slow and rather difficult to assess owing to her inability to walk alone. Marked valgus deformity of the feet necessitated a period of immobilization after which she needed irons, and 18 months had passed before she was able to dispense with this aid. By then she was able to walk well and even turn somersaults. She could accompany her mother shopping, walking slowly, and climb stairs. There was a striking improvement in her mentality and she became much more alert and showed a fair aptitude to learn. The cyanosis decreased slowly, but was always present to a slight degree. Six weeks after operation haemoglobin was 85% and red cells 4,700,000. The heart became larger and a machinery murmur became audible in addition to the pre-existing systolic bruit.

She continued satisfactorily until December, 1950, when she contracted infective hepatitis. After two weeks she seemed quite well again and remained so until mid-January, 1951, when she had a febrile respiratory infection. From then until the time of admission to hospital on February 12 she complained of lassitude and lost weight. On admission, at the age of 8, she was very thin (weight 32 lb.), and showed a mixture of pallor and cyanosis. The temperature was normal, pulse 120, respirations 30. The clubbing of fingers and toes had changed little from when first seen. Dental caries and marked gingivitis were present, and a few purpuric spots were noted on the right side of the chest. The operation scar was sound. The heart was enlarged, the apex beat being ½ in. outside the mid-clavicular line in the fifth interspace. A harsh systolic murmur, maximal at the second and third interspaces, and a continuous murmur at the first and second right interspaces were heard. Blood pressure was 105/70. There were diminished breath sounds at the right base and basal râles in both lungs. The spleen was enlarged two fingerbreadths below the costal margin.

No other abnormalities were noted.

Special investigations showed the following: Hb. 65%; red cells 3,800,000; leucocytes 11,800 (polymorphs 61%, lymphocytes 35%, monocytes 4%). The E.S.R. was 15 mm. in the first hour. The bleeding time was 4½ minutes, and the coagulation time 7 minutes. Platelets were 50,000 per c.mm.

The urine on repeated examination showed a trace of albumin but no red cells.

A blood culture showed a growth of non-haemolytic streptococci twice in four days.

Serum bilirubin was 7 mg. per litre.

The Van den Bergh test gave a faint positive indirect reaction.

Serum protein was 3·9 g.%, albumin 1·5 g.%, globulin 2·4 g.%.

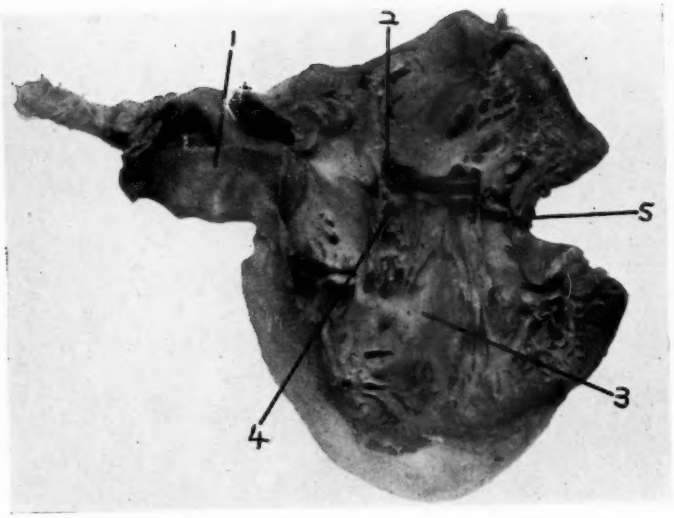


FIG. 2.—Anterior view of the heart.

1 = aorta; 2 = pulmonary orifice; 3 = ridge representing interventricular septum; 4 = right auriculo-ventricular orifice; 5 = left auriculo-ventricular orifice.

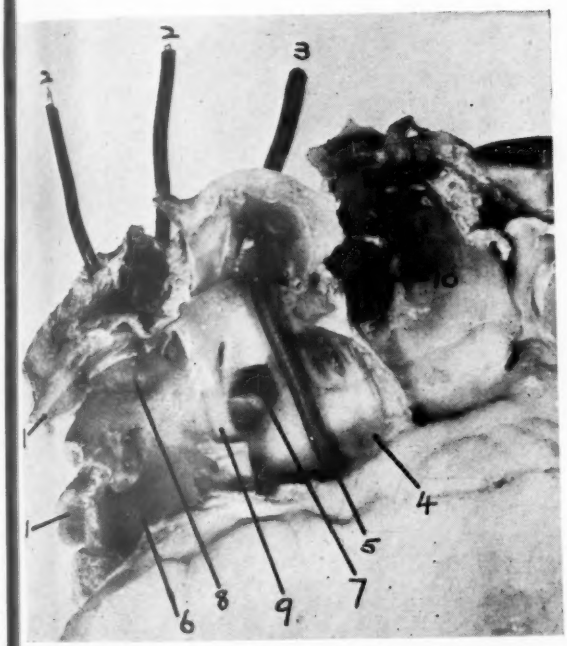
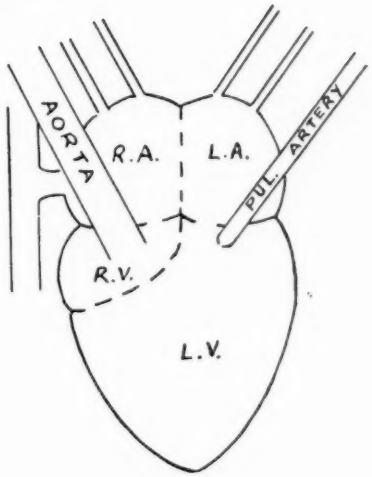


FIG. 3.—Posterior view of the heart with auricle opened.

1 = left pulmonary veins; 2 = right pulmonary veins; 3 = superior vena cava; 4 = inferior vena cava; 5 = right auriculo-ventricular orifice; 6 = left auriculo-ventricular orifice; 7 = right auricular appendage; 8 = left auricular appendage; 9 = rudimentary interauricular septum; 10 = mycotic aneurysm of pulmonary artery)



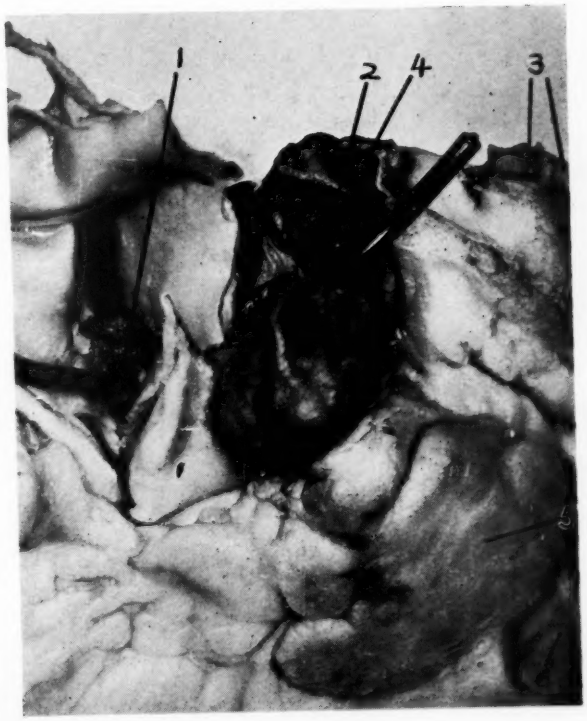


FIG. 4.—Superior view of the heart.

1 = Pulmonary artery with wire through pulmonary valve; 2 = rupture in mycotic aneurysm; 3 = right pulmonary veins; 4 = superior vena cava; 5 = right auricular appendage; 6 = left auricular appendage.

The formol gel reaction was negative.

The serum alkaline phosphatase level was 10 King-Armstrong units.

A radiograph of the chest showed a confluent, mottled area of opacities at the right base with an area of infiltration in the right mid-zone.

Penicillin, 200,000 units 4-hourly, was begun, but petechiae continued to appear for some days and mild pyrexia up to 100° started on February 28. The face became slightly oedematous. However, the child's general condition seemed better and she took her food well. On March 4 she sat up in bed suddenly, collapsed, and was dead in about a minute.

Necropsy Findings. The relevant findings were confined to the cardiovascular system. On opening the pericardium the sac was found to be full of blood which had escaped from a ruptured mycotic aneurysm the size of a kidney bean on the pulmonary artery just proximal to its bifurcation. The artificial ductus was found to be patent and not diseased. The heart was considerably enlarged and consisted mainly of an hypertrophied and dilated left ventricle. The abnormalities found were as follows: (1) transposition of the great vessels with a right aortic arch; (2) gross enlargement of the left ventricle; (3) a diminutive right ventricle; (4) virtual absence of the inter-ventricular septum which was represented by a narrow fold; (5) valvular pulmonary stenosis; (6) both auricles small and separated only by a rudimentary fold similar to that between the two ventricles; (7) two of the pulmonary veins drained into the right auricle and two into the left; (8) the superior and inferior venae cavae entered the right auricle as a common vessel; (9) a mass of vegetations was present on the right auriculo-ventricular valve and on the stenosed pulmonary valve. The auriculo-ventricular valves appeared normal and the coronary arteries were normally placed. Thus the heart was functionally bilocular.

Discussion

Functionally, this child possessed a single ventricle from which both great vessels sprang. In such a patient it is of importance to know whether the pulmonary artery is stenosed or not, for in the latter case the pressure in this vessel will be as great or greater than that in the aorta with the result that a pulmonary-systemic anastomosis will be of no benefit, while in the former the pulmonary blood supply will be increased by such an operation and the patient will benefit. In this instance the absence of the pulmonary cone and clear lung fields favoured a pulmonary stenosis, although the other abnormalities were not diagnosed, and the operation caused considerable improvement.

Hurst, Gleason and Schemm in 1949 reported a case of subacute bacterial endocarditis in a girl of 10, two years after Blalock had operated upon her for the tetralogy of Fallot. This girl recovered, and they mentioned a personal communication from Taussig that she had seen such a complication in four cases up to that date, but gave no details. No other examples appear to have been recorded since then.

Summary

A case is described in which infective endocarditis caused death by rupture of a mycotic aneurysm of the pulmonary artery two and a half years after a Taussig-Blalock operation had been performed.

Post-mortem examination showed that the heart was functionally bilocular and that there was transposition of the great vessels.

We are indebted to Dr. Alan Booth, radiologist to the Royal Hospital, Wolverhampton, for help in the interpretation of the radiographs, and to Mr. D. R. Paton, of the Photographic Department of the Royal Hospital, for the photographs.

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METHODS OF ASSESSING THERAPY IN CHOREA WITH SPECIAL REFERENCE TO THE USE OF A.C.T.H.

BY

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Like other manifestations of the rheumatic state chorea is subject to spontaneous remissions and relapses which make the assessment of the action of any particular therapy notoriously difficult. Furthermore, objective measurements of the degree of chorea seem necessary to confirm clinical impressions of an increase or decrease of chorea. With this in mind certain objective methods of assessing the action of therapy in chorea have been worked out, and are presented together with some results of their application to the treatment of chorea with A.C.T.H. Treatment may alter the severity of the duration of chorea. Its severity has been estimated in three ways: first, by clinical grading, secondly, by dexterity tests, thirdly, by means of a kinetic bed. In addition, certain permanent records of the choreic state have been developed which facilitate subsequent assessment of changes.

Clinical Grading

The following clinical grades are based on daily observation, with special attention to movement of outstretched hands, steadiness of grip, speech and emotional lability:—Grade 0=no chorea; grade 1=just discernible chorea; grade 2=all cases of chorea between grades 1 and 3; grade 3=severe chorea where the patient is crippled by involuntary movements and cooperates with difficulty or not at all in the writing and dexterity tests.

Dexterity Tests

A standard peg-board* with 100 small plastic pegs is used. The time taken by the patient to fit the pegs into the board is used as an index of the severity of chorea (Fig. 1). An arbitrary upper limit of normal of four minutes has been included in the diagrams.

Kinetic Bed

This instrument gives a semiquantitative record of the movements of a choreic child in bed. An elongated pneumatic rubber cushion, 6 in. wide × 3 ft. long, is placed transversely across the bed at the level of the elbows and upper lumbar vertebrae. The air in the cushion is connected by a rubber tube to a manometer and a rubber tambour. The cushion is inflated to a standard pressure (between 5 and 10 cm. of water) with the child lying in bed. Movement of the child upon the cushion causes

FIG. 1.—Patient doing dexterity test.

* Obtainable from Dryad Handicrafts Ltd., 22 Bloomsbury Street, W.C.1.

changes in pressure in the tambour. The movements of the tambour (Fig. 2) rotate a wheel by a ratchet mechanism. To the wheel is attached a contact which once every complete rotation makes and breaks an electrical circuit to a counter. A special feature of this mechanism is the very small advance of the wheel with each step of the ratchet. The least change of pressure in the tambour which can be recorded will cause an advance of the wheel one hundredth of that caused by the largest change in pressure. Thus the instrument adds up not only the number but the force of the movements. The kinetic bed score is in arbitrary units, but an indication of its meaning is provided by some tests with a normal 10-year-old girl. In her, the following repeated movements caused a score of one unit on the kinetic bed: (1) one arm lifted and dropped—49 times; (2) raising of body from hips up to a resting position on one elbow—20 times; (3) transfer of small article from locker to bed—45 times; (4) lifting both hips to straighten nightdress —7 times.

The choreic child lies on the kinetic bed throughout the 24 hours. Readings are taken at 7 a.m. and 7 p.m. The day score is always larger than the night score, and both day and night scores may reach high figures in very choreic children; for example, one child caused a score of 300 (day) and 60 (night). Non-choreic children, even if active in bed, rarely score more than 20 (day) and 5 (night). A representative arbitrary normal reading of 10 for the day score has been included in the diagrams.

Permanent Records

We have taken cine films of chorea and have recorded the choreic voice, but we have found that simpler tests give equally satisfactory results. One of these is a standard writing test, in which the patient signs her name and copies a simple design, and another is a 30-second exposure photograph of the choreic child with a flash lamp bulb attached to her finger which she attempts to keep still (Fig. 3).

TABLE 1

ANALYSIS OF DURATION OF CHOREA IN 90 PATIENT-ATTACKS*

Interval after Onset (weeks)	Total (*a*) Choreic at Beginning of Interval	No. (*b*) Losing Chorea during Interval	Recovery Rate ($b/a \times 100$) in Interval
0–4	90	7	7·8
4–8	83	18	21·7
8–12	65	14	21·5
12–16	51	15	29·5
16–20	36	7	19·5
20–24	29	5	17·3
24–28	24	4	16·7
28+	20	20	(100)

* Treatment by rest in bed only, apart from a few who received symptomatic treatment with sedatives or salicylates in small amounts.

Duration of Chorea.

This battery of tests can help in the evaluation of changes in severity of chorea under treatment, but improvement in the duration of chorea under treatment can only be assessed by comparison with the duration without treatment. Furthermore, the expected recovery rate varies with the previous

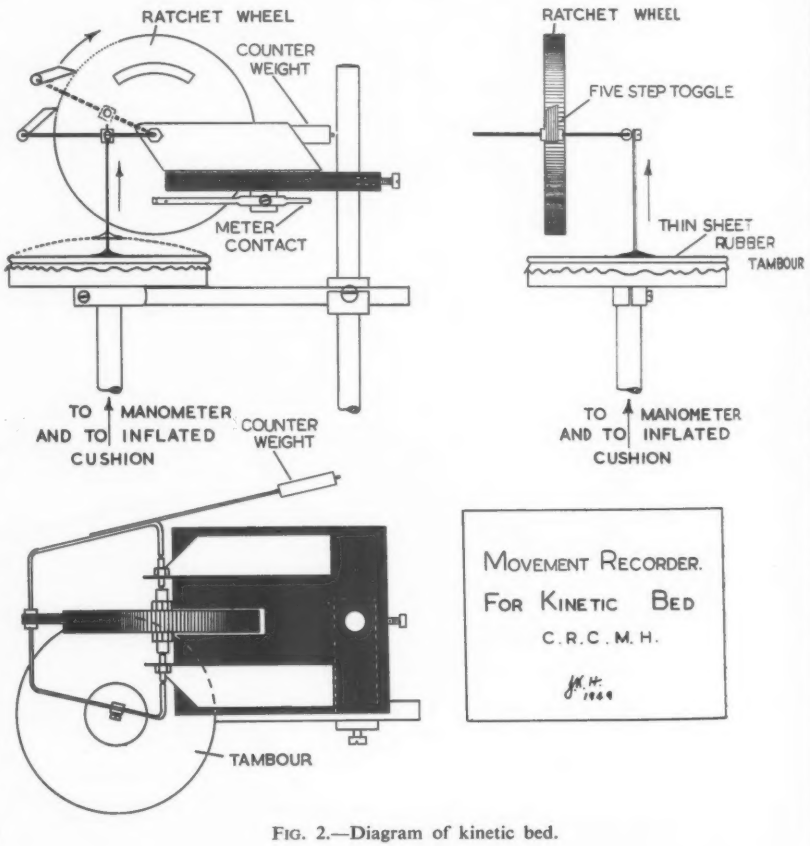

FIG. 2.—Diagram of kinetic bed.

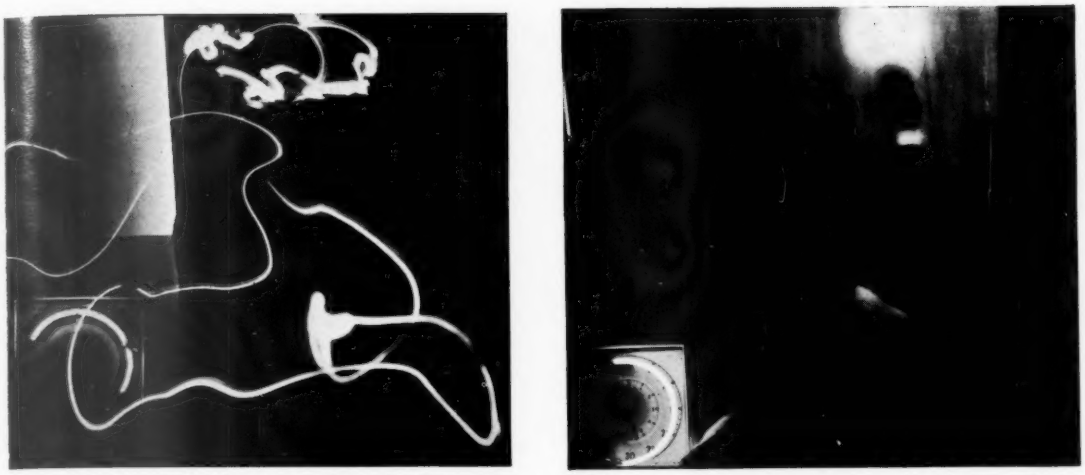

FIG. 3.—Light-trace photograph of patient J.K. (30-second exposure) before and after spontaneous recovery in 14 days. A flash lamp bulb has been attached to the index finger. The patient is attempting to keep her finger still. The left-hand photograph shows grade III and the right hand one grade I chorea.

duration of the disease. We have, therefore, analysed 90 patient-attacks of chorea of which we have records of the dates of onset and of recovery, (Table 1) and have therefrom constructed a 'life table' of the duration of the disease. It will be used for comparison with the recovery rate in a series of children receiving special treatment. This method is, of course, valid if there is no change in the nature of the disease.

Fig. 4 shows the recovery rate in four-week periods. For this series the expectation of recovery is least in the first month and greatest in the fourth, by the end of which period nearly two-thirds of the cases had recovered.

Discussion

Clinical grading is relatively simple, and after a little practice independent observers give the same grading. Grade 2, of course, embraces a wide range of severity of chorea, but this does not matter in assessing therapy, since a drug is not likely to be of much use unless it can cause big changes in the patient's condition.

Dexterity test times are useful in the more severe cases, and follow clinical grading quite well. They are increased by sedation. Because of the simplicity of this test the 'learning factor' can quickly be eliminated by one or two preliminary trials.

The kinetic bed score records all movements, both voluntary and choreic. The score varies with the grade of chorea (Fig. 5), but also with several other factors such as the inflation pressure of the bag, the age, body weight, alertness of the patient, the permitted activity of the patient and the

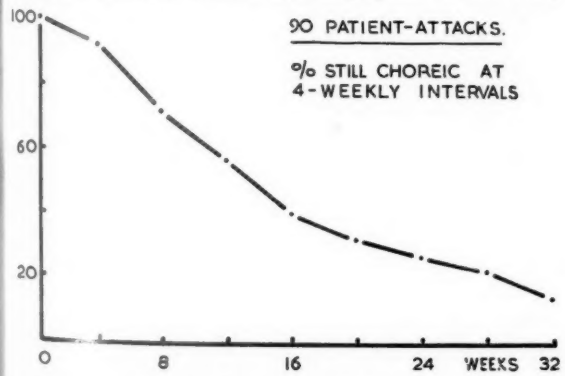

FIG. 4.—Recovery rate of chorea.

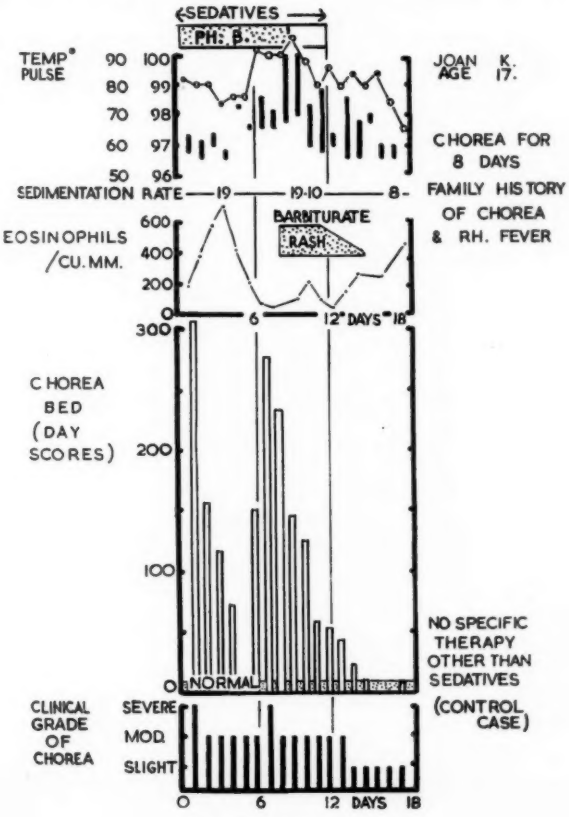

FIG. 5.—Chart of J.K.

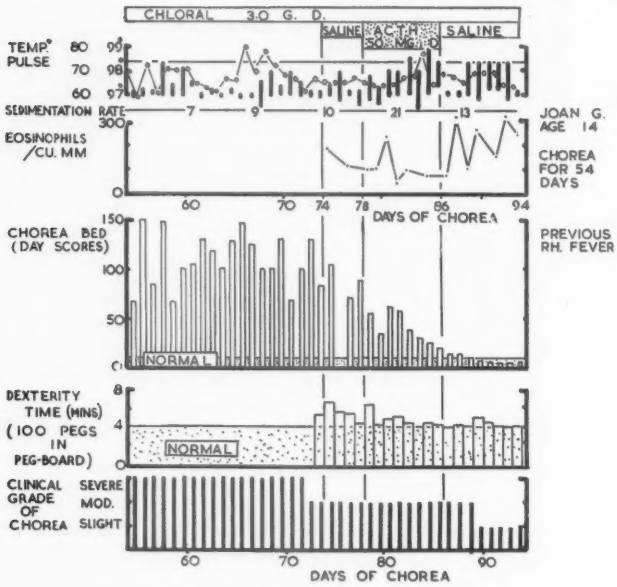

FIG. 6.—Chart of J.G.

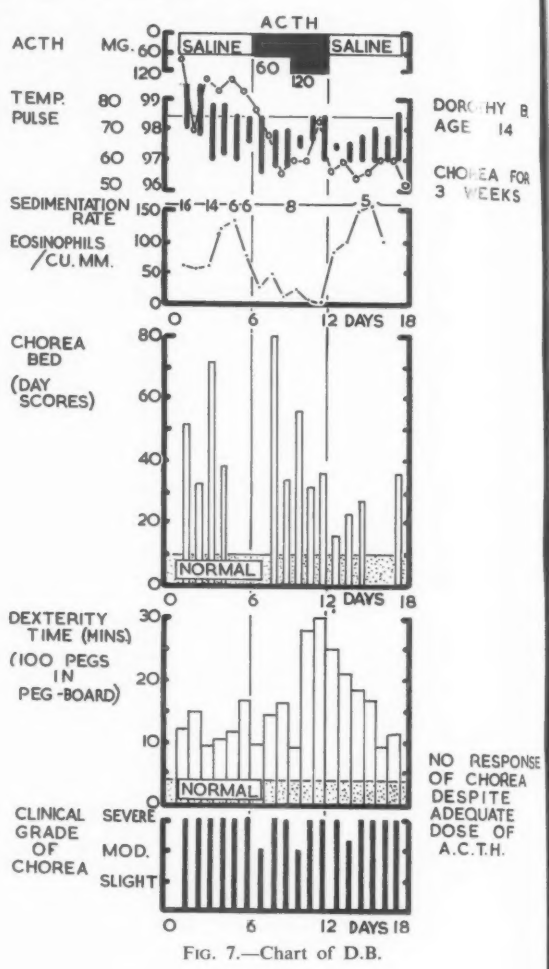

FIG. 7.—Chart of D.B.

amount of sedation. The kinetic bed has been used for comparing the same patient under standard conditions at different times, but not for comparing different patients; thus the day score in the same patient has varied from 300 to 10 during spontaneous recovery from severe chorea. 'Paralytic' chorea, and patients, such as M.B. (Fig. 9), who are severely ill, may give normal scores despite severe chorea. The principle of a recording bed has previously been used in connexion with schizophrenia (Gjessing, 1939).

The use of these tests has confirmed the existence of varying functional patterns of chorea. Thus in some patients there is little interference with voluntary movement, as shown by normal dexterity, but a great increase in movement at rest, as shown by the kinetic bed score (patient J.G.). On the other hand there may be gross interference with dexterity and little increase of movement at rest (patient D.B.).

Results with A.C.T.H.

This study was prompted by an early report (Massell, Warren, Sturgis, Hall and Craige, 1950) where it was mentioned that A.C.T.H. appeared to benefit a case of chorea, and by encouraging results from our own first case who recovered from severe chorea of 78 days' duration during an eight-day course of A.C.T.H. therapy. Since that time another favourable report has appeared (Bunim, 1951).

It is not possible to conclude that A.C.T.H. or any other drug is the cause of a decrease in chorea, since chorea is a disease which can improve spontaneously, unless the natural recovery rate is significantly lower than the treated recovery rate under similar conditions. On the other hand, it is possible to conclude that A.C.T.H. does *not* benefit chorea if a small number of cases adequately treated do not respond. This has been found in the present small series.

Patients were selected who had severe or moderately severe chorea. During the study they were kept in bed in single-bed wards. Sedatives were avoided as far as possible. There was first a period, usually six days, in which control readings were made and saline injections given. A.C.T.H. was then substituted for saline. After six or eight days of A.C.T.H. saline injections were again given. These changes were made without the patient's knowledge. The degree of chorea was assessed as above, the effectiveness of the A.C.T.H. by daily direct eosinophil counts on capillary blood

(Randolph, 1944) four hours after the first daily injection. All measurements were made at the same time of day. In some instances total urinary 17-ketosteroid excretion was followed.

Case Reports

Case 1. J.G., aged 14 (Fig. 6), suddenly developed a fourth attack of chorea on April 9, 1950. She showed severe chorea for 54 days before A.C.T.H. treatment was started, despite chloral hydrate sedation. She was emotional, dirty, disorientated and sometimes manic. A week before saline injections there was some improvement in her emotional state but no objective change. For four days saline injections were given. There was further slight improvement. During the next eight days she received A.C.T.H. (50 mg./day) and improved remarkably. When A.C.T.H. was stopped, improvement continued and there was no relapse. Chorea did not finally disappear until four weeks later. Our final impression was that we had treated this girl when she was recovering naturally.

Case 2. D.B., an intelligent girl of 14 (Fig. 7), had been previously admitted to this hospital for rheumatic fever and carditis, and was readmitted for severe chorea of three weeks' duration. She was given saline injections for six days. During this time her slightly raised temperature, pulse and sedimentation rates fell to normal, her kinetic bed score was moderately raised, and her chorea, which was severe, showed a gross interference

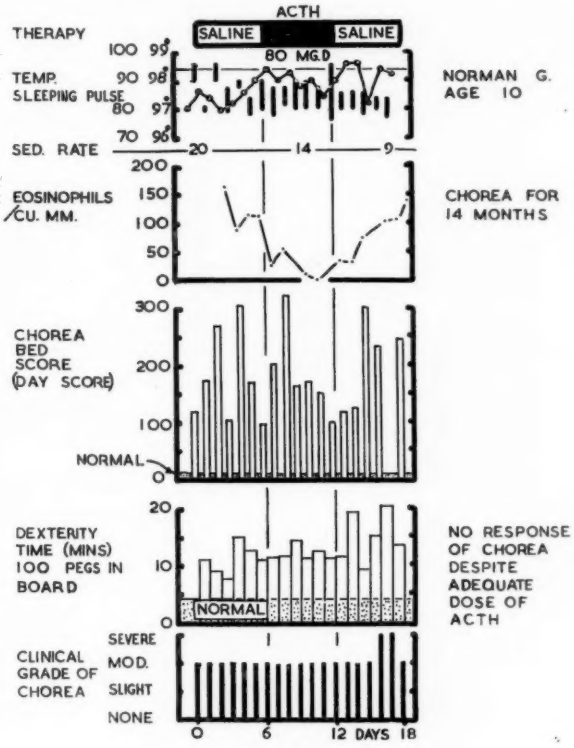

FIG. 8.—Chart of N.G. (Case 3).

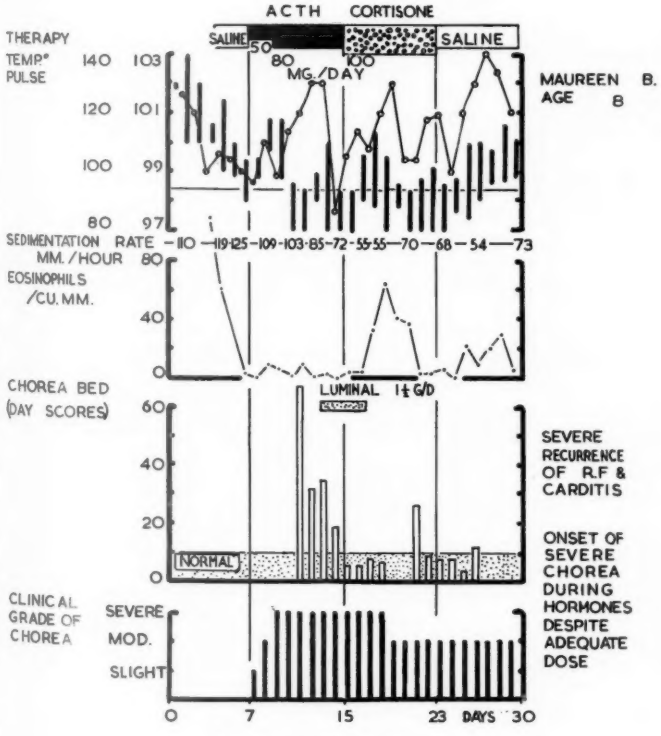

FIG. 9.—Chart of M.B. (Case 4).

with attempted voluntary movement in the dexterity test. She could just write a recognizable signature. She was not emotionally disturbed. For the next three days she received A.C.T.H. (60 mg./daily), followed by three days at 120 mg./day. There was no improvement; on the contrary movements were so choreic that she was unable to hold a pencil to sign her name, and took up to 30 minutes to complete a dexterity test. Kinetic bed scores remained raised. At the same time, a low circulating eosinophil count showed that the dose was adequate.

During the next six days with saline injections there was little clinical change although kinetic bed scores and dexterity test times improved a little. Chorea began to improve in the following week and finally stopped in six weeks.

Case 3. N.G., a boy of 10 (Fig. 8), had had grade 1 chorea for 14 months, which relapsed to grade 2 while he was in hospital. He was followed in a similar way to Case 2 and showed much the same results. Despite a satisfactory fall in circulating eosinophils during A.C.T.H. treatment, there was no improvement in the clinical grade, dexterity or kinetic bed scores. He still shows grade 2 chorea five weeks after A.C.T.H. treatment.

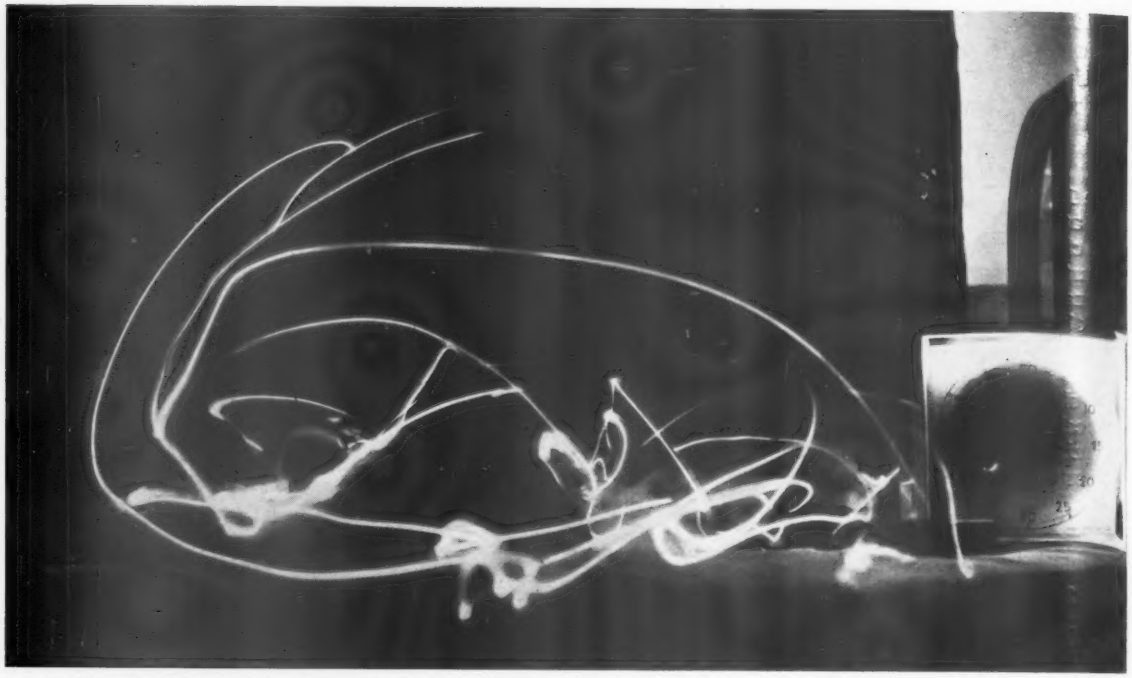

FIG. 10.—Chorea trace photograph of M.B. demonstrating grade III chorea at eighth day of A.C.T.H. therapy.

Case 4. M.B., aged 8 (Fig. 9) was admitted to this hospital with a recurrence of rheumatic fever and carditis. She was severely ill and developed pericardial and pleural effusions and congestive cardiac failure. The sedimentation rate was 110 mm. in one hour (Westergren). There was no chorea. She was given 50 mg. A.C.T.H. daily from the seventh day of admission. This dose did not control fever and after three days was increased to 80 mg. daily for five days. Chorea first appeared on the evening of the first day of A.C.T.H. therapy and increased rapidly in severity. Luminal, gr. 1½ daily, was given from the sixth day of A.C.T.H. for four days. She was next given cortisone, 100 mg. daily, for eight days. There was only slight improvement in chorea. That doses of these hormones were adequate was shown by the falls in temperature and sedimentation rate. The eosinophil count had already fallen to a low level from heart failure before treatment. This low level was maintained throughout treatment, apart from a transient 'release rise' when cortisone was substituted for A.C.T.H. The kinetic bed score was not reliable because she was so weak and ill that her movements, although frequent, were too feeble to cause much change in pressure in the inflated rubber cushion on which she was lying. The true state of her chorea is shown more clearly by the 30-second photograph (Fig. 10) taken on the last day of A.C.T.H. treatment. The total duration of chorea in this girl was 13 weeks.

Summary and Conclusion

Methods of assessing the effects of therapy on the severity and duration of chorea are presented. A.C.T.H. treatment has been followed by these methods in four patients. The doses used were as great as, or greater than, those which in our hands previously had produced rapid improvement in other manifestations of the rheumatic state. A.C.T.H. in this dosage does not benefit Sydenham's chorea.

Acknowledgement and thanks are due to various colleagues, especially Mr. John Harrison who designed and constructed the 'kinetic bed' counter, and to Mr. Peter Fiske, A.R.P.S., who took the photographs. The A.C.T.H. used was allocated by the M.R.C. Clinical Trials Committee from a gift made by Messrs. Armour Brothers Ltd., Chicago, Illinois.

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CONGENITAL TUBERCULOSIS

BY

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Congenital tuberculosis may be defined as tuberculosis occurring in infants as a result of infection with *Myco. tuberculosis* during intra-uterine life.

The condition has been the subject of much controversy in the past; some have refused to accept it as a pathological entity, others, such as Baumgarten (1925), have ascribed many cases of tuberculosis occurring in young persons to a congenital origin. However, the present century has seen the establishment of the disease as a rare but well defined entity. It appears in two main forms: one in which the lesions are most prominent in the lungs and which is thought to be due to aspiration of infected amniotic fluid by the foetus, the other in which the earliest lesion is found in the liver and its regional lymph nodes. A third form, in which death of the foetus occurs before the development of macroscopic lesions, is known as tuberculous bacillaemia.

Two essential facts must be clearly established in every example of the disease. First, it must be proved to be a result of tuberculous infection: secondly, the infection must have occurred during intra-uterine life. A number of authors have laid down conditions which each reported case must satisfy, and of these Beitzke (1935) appears to have provided the most satisfactory criteria. He proposed that a case should not be accepted as congenital tuberculosis unless (1) the presence of *Myco. tuberculosis* in the infant was proved, and (2) either (*a*) a primary tuberculous complex was present in the liver, or (*b*) the tuberculous lesions were present at birth, or (*c*) extra-uterine infection could be excluded with certainty.

Using these criteria, Beitzke (1935) reviewed the literature and accepted 61 cases of congenital tuberculosis and 40 of tuberculous bacillaemia. Hughesdon (1946), using the same criteria as Beitzke, accepted a further six cases of congenital tuberculosis, one case of tuberculous bacillaemia and added four cases of congenital tuberculosis of her own.

Since then I have found 18 published cases for which a congenital origin was claimed, of which 10 satisfy the conditions required by Beitzke, Jordan and Spencer (1949), Hertzog, Chapman and Herring (1949), Ballabriga Aguado (1950), Germain, André and Marty (1950), Pagel and Hall (1946), Aufdermaur (1947), Daamen (1947), Danjou (1947), Wallgren (1948) and Debré, Furiet-Laforet and Royer (1948). To date 83 cases of congenital tuberculosis and 41 cases of tuberculous bacillaemia have been described. Of these, nine have occurred in the British Isles: those of Andrewes (1903), Morley (1929), Price (1937), Davin-Power (1941), Hughesdon (1946) and Jordan and Spencer (1949). A further case of congenital tuberculosis is presented here.

Case Report

The child, a girl, was born after 40 weeks' gestation and weighed 7 lb. at birth. She appeared well until just before death, having taken her feeds satisfactorily and almost regained her birth weight when, on the eighth day, attacks of cyanosis occurred and she died suddenly during one of them. There had been no clinical reason to suspect that she was suffering from tuberculosis. From birth she was isolated from her mother, and was not subsequently in contact with her.

Necropsy Report. The body was well nourished and without congenital abnormality. The skin was cyanotic.

HEART AND LUNGS. The heart was normal. Each pleural cavity contained 5 ml. of clear, yellow fluid. Grey-yellow tubercles measuring 1 to 3 mm. in diameter were present beneath the visceral pleura of all lobes of both lungs. In the substance of the lung were numerous tubercles of 1 to 5 mm. in diameter (Fig. 1). The tracheo-bronchial glands were not enlarged. The right lung weighed 62 g., the left 58 g.

ABDOMEN. There were 10 ml. of clear yellow fluid in the peritoneal cavity. White exudate was present on the peritoneal surface of the spleen, causing it to be matted to coils of small intestine. The mesenteric glands were not enlarged.

LIVER. The liver (260 g.) contained a number of grey-yellow tubercles, measuring 1 to 3 mm. in diameter,

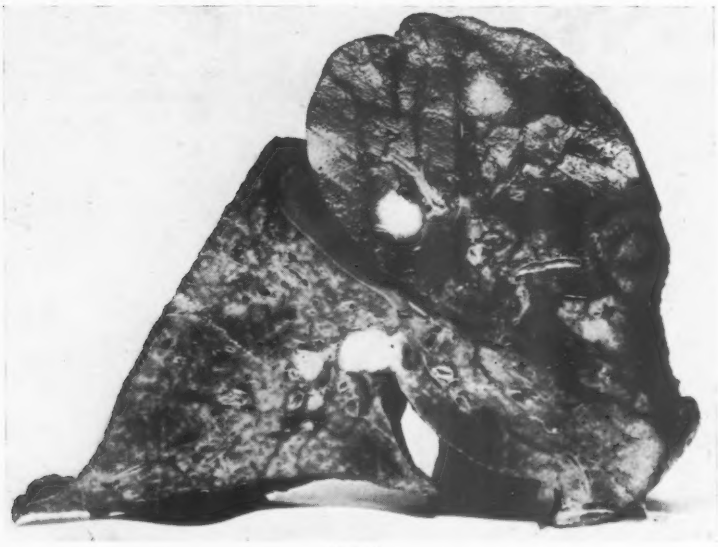

FIG. 1.

FIG. 1.—Cut section of lung.

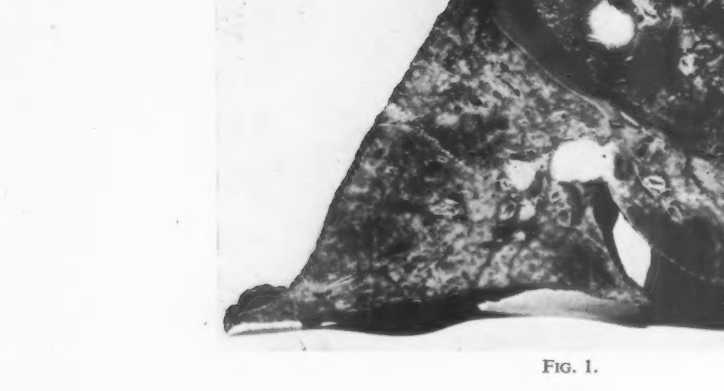

FIG. 2.

FIG. 2.—The liver showing at the porta hepatis the caseous tuberculous glands, part of which has been removed.

FIG. 3.—The spleen showing tubercles of various sizes.

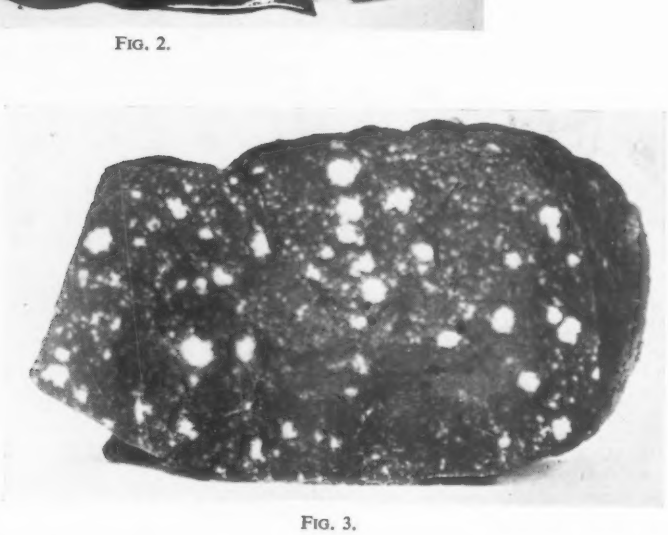

FIG. 3.

beneath its peritoneal surface and also within its substance. A larger area of caseation, measuring 0·4 cm. ×1 cm. was present in the right lobe. The glands of the porta hepatis were enlarged, measuring 3 cm.× 2·5 cm.×1·5 cm. They were not attached directly to the liver and on section presented the appearance of caseous tuberculous glands (Fig. 2).

SPLEEN. The spleen (35 g.) was engorged and contained large numbers of grey-yellow tubercles of various sizes from 0·1 cm. to 0·5 cm. in diameter. The organ measured 7·5 cm.×4 cm.×3 cm. (Fig. 3).

BRAIN. The hemispheres appeared to be congested.

The other organs of the body revealed no macroscopic abnormality.

The placenta was not available for study. It weighed 1 lb. 12 oz., and was reported as having appeared normal.

On microscopical examination the pattern of the liver was normal. The liver cells showed marked cloudy swelling and some fatty degeneration. Scattered throughout the liver substance were areas of necrosis, complete at the centre and less complete at the periphery. In the outskirts of these were a few lymphocytes and plasma cells but they did not form complete rings. No giant cells were seen. Ziehl-Neelsen staining revealed many bacilli, having the morphological appearance of *Myco. tuberculosis*, within the necrotic areas (Figs. 4 and 5).

The microscopic picture confirmed the caseation seen macroscopically in the nodes of the porta hepatis. There were no giant cells. A direct smear from the cut surface of the node showed a mass of *Myco. tuberculosis* (Fig. 6).

The spleen contained necrotic areas in which were masses of *Myco. tuberculosis*.

The lungs were generally congested. Scattered throughout the substance were areas of necrosis similar to those in the liver.

The following details about the mother were kindly supplied by Dr. Mason:

Mrs. Irene W., aged 24, was well until November, 1949, when, during the fifth month of her second pregnancy, she developed a left pleural effusion. One pint of clear fluid containing only lymphocytes was aspirated on December 1 and on December 8.

On February 6, 1950, the patient was admitted to hospital for observation before her confinement. She was symptomless and apyrexial, with an erythrocyte sedimentation rate of 18 mm. in one hour (Westergren). She remained thus until April 17 when the evening temperature rose to 99° F. She went into labour on April 19, and during the next eight days the evening temperature varied between 99° and 101°. On April 29 she started a course of 1 g. of streptomycin and 15 g. of para-amino-salicylic acid daily. From June 15 the evening pyrexia ceased. She had completed a course of 120 g. of streptomycin by August 27 when she stated that she felt well. The erythrocyte sedimentation rate then was 4 mm. in one hour (Westergren).

A radiograph of the chest on April 27 showed a finely granular appearance of the lung fields which suggested early miliary tuberculosis. This mottling had cleared by June 29.

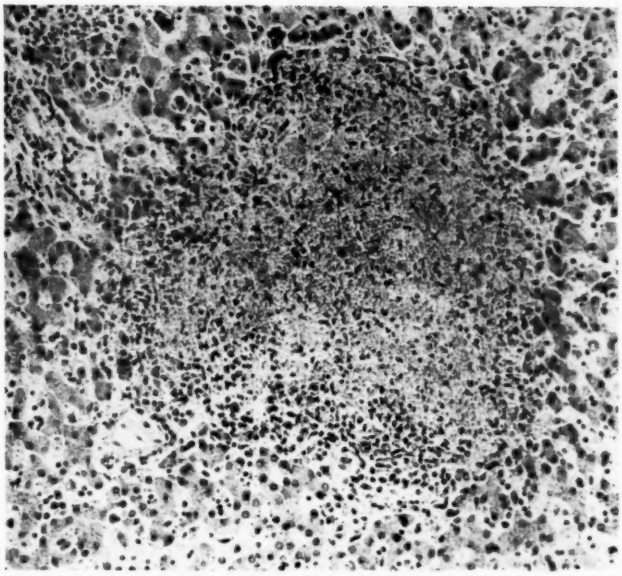

FIG. 4.—Section of liver ×100 showing a necrotic tubercle (haematoxylin and eosin).

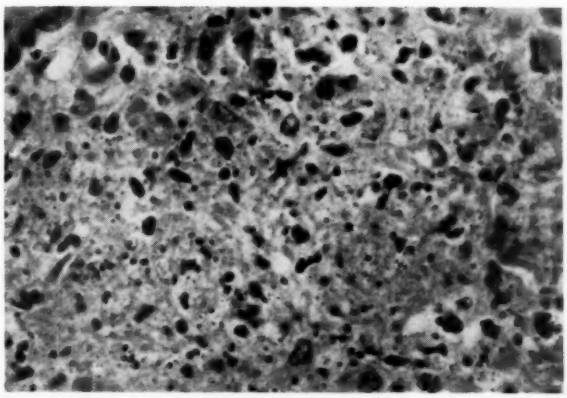

FIG. 5.—Higher power view of the centre of the necrotic area of Fig. 4 showing fragmentation of nuclei and absence of cell outlines (haematoxylin and eosin).

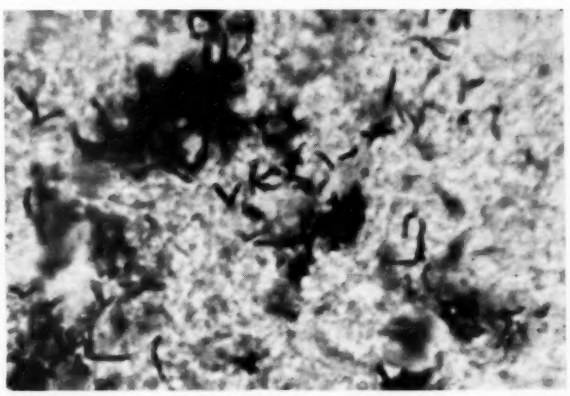

FIG. 6.—High power (×1200) view of gland of porta hepatis stained by Ziehl-Neelson method showing numerous *Myco. tuberculosis*.

She was discharged symptomless on October 19, 1950, and has remained well.

Discussion

The case reported appears to be without doubt congenital. The presence of caseating tuberculous glands in the porta hepatis and a caseous area in the right lobe of the liver suggests that this was a primary liver complex from which a late miliary spread had taken place, as often in congenital tuberculosis the infant appears well at birth and subsequently dies rapidly with miliary dissemination.

The microscopic appearance of the lesions was similar to that described by Pagel and Price (1943) and Hughesdon (1946) and corresponded to the description of the 'soft tubercle' by Rich and McCordock (1929). It is noteworthy that the lesions showed local necrosis with very little tissue reaction; there were neither giant cell formation nor rings of epitheloid cells and lymphocytes. Such lesions have been described where the tissues have been overwhelmed by *Myco. tuberculosis*.

The mothers of infants suffering from congenital tuberculosis usually have advanced tuberculosis, often of the lungs, and the mothers frequently die soon after parturition. However, in some instances, such as the cases of Reichle and Wheelock (1939), Whitman and Greene (1922), Chiari (1932) and Hughesdon (1946), the mothers remained well, while in those of Morley (1929) and Söderström (1932) there appeared to be no evidence of maternal tuberculosis at all. In the case of Pagel and Hall (1946), although originally the mother was reported well, in a later publication (1948) the mother was reported as having subsequently developed fatal disseminated tuberculosis.

The present case is the first which I have been able to find where the mother was treated with streptomycin. It seems likely that maternal haematogenous spread occurred at or immediately following parturition and responded to antibiotic treatment.

Pathogenesis of Congenital Tuberculosis. Whitman and Greene (1922) were of the opinion that congenital tuberculosis was transmitted from the father by way of the spermatozoa, but there is now little support for this hypothesis. It is unlikely because genital tuberculosis in the male often leads to sterility, and because infection of the foetus at the time of conception would almost certainly lead to abortion. The latter contention is supported by the observation that tuberculosis of the placenta has never been found before the fourth month of pregnancy.

Calmette and Valtis (1930) tried to prove the existence of an ultra-virus as an alternative form of *Myco. tuberculosis*. It was suggested that in such a form the bacillus might cross the placental barrier and infect the growing foetus. This hypothesis has now been firmly refuted by a number of workers and will not be discussed further.

Mothers of infants suffering from congenital tuberculosis usually have advanced tuberculosis. The maternal history may contain an incident which would have been likely to lead to bacillaemia, such as an acute flare-up of a quiescent tuberculous lesion, or the onset of miliary tuberculosis. Loewenstein (1935) found a positive tuberculous blood culture in 11 of 59 parturient women suffering from tuberculosis. Infection of the placenta, which is the first step in infecting the foetus, probably occurs during maternal tuberculous bacillaemia.

However, there remain a few cases such as those of Morley (1929) and Söderström (1932), in which the mother was reported clinically and radiologically free from tuberculosis. It may well be that in such instances the mother was suffering from tuberculous endometritis from which direct spread to the placenta occurred. O'Brien and Lawlor (1947), amongst others, have shown that tuberculous endometritis may be discovered only by careful search of uterine curettings, and such a search was not undertaken in either of the two cases cited. The majority of women suffering from tuberculous endometritis are sterile, a fact which may explain the rarity of congenital tuberculosis where the mother is apparently healthy. According to Gofton (1937), tuberculous pyometritis is common in the dams of calves found to have congenital tuberculosis, and Reichle and Wheelock (1939) and Hertzog *et al.* (1949) all reported maternal tuberculous endometritis in their cases of congenital tuberculosis.

Vaccaro and Paredes (1947), from experimental studies on animals, believe that *Myco. tuberculosis* may cross the placental barrier without causing a lesion. However, this is not borne out by a study of human congenital tuberculosis. Since the condition is often unsuspected at birth the placenta has been carefully examined in a relatively small proportion of cases only; in those cases where it has been studied microscopically caseous tuberculosis has always been found.

Seigel and Singer (1935) have shown that placental infection begins as a thrombus containing *Myco. tuberculosis* in an intervillous space, and later develops into a necrotic tubercle. Often thrombosis of the foetal vessels draining the area occurs and no disease is transmitted to the foetus; this explains the fact that placental tuberculosis is much commoner than congenital tuberculosis. For instance, Schmorl and Geipel (1904) found tuberculous lesions in nine of 20 placentas belonging to tuberculous mothers.

Infection from the placenta to the foetus may occur theoretically in one or more of three ways: (1) by direct infection of the amniotic fluid which is then ingested or inhaled by the foetus; (2) by haematogenous spread; (3) by lymphatic spread.

INFECTION FROM AMNIOTIC FLUID. Foetal infection by aspiration of infected amniotic fluid probably occurs in a small number of cases. Schmorl and Geipel (1904) described tuberculosis of the placenta infecting the amniotic fluid by rupture of a caseous focus through the amniotic membrane. Since then, Reichle and Wheelock (1939) in a review of the literature accepted seven cases of the aspiration type of congenital tuberculosis and added one of their own. Often infection appears to have occurred during parturition when the infant became partially asphyxiated in the birth canal and began to breathe before delivery was complete.

Aspiration of amniotic fluid before parturition is also possible, since Snyder and Rosenfeld (1937) have shown that respiratory movements occur in foetal rabbits during intra-uterine life. Although this contention has been challenged by Whitehead *et al.* (1942), the work of Davis and Potter (1946) appears to have established without doubt the validity of intra-uterine respiratory movements.

Infants infected by aspiration of infected amniotic fluid are found on post-mortem examination to have miliary tuberculosis confined to the lungs. Often death occurs before the development of caseation in the regional nodes.

HAEMATOGENOUS SPREAD. In most of the reported cases congenital tuberculosis probably occurred as a result of haematogenous spread along the umbilical vein. Foetal tuberculous bacillaemia has been demonstrated by a number of workers. For example, Siegel and Singer (1935) cultured the cord blood of 15 infants born to mothers suffering from advanced tuberculosis; they obtained a positive result in one infant which died shortly afterwards and in which the heart blood also gave a positive culture. Warthin and Cowie (1904) demonstrated thrombi full of *Myco. tuberculosis* in the liver of an infant stillborn to a tuberculous mother.

In some instances, such as that of Whitman and Greene (1922), the tuberculous bacillaemia causes miliary tuberculosis without a primary complex, while in others a primary complex occurs, usually in the liver and sometimes in the liver and lungs. Siegel (1934), reviewing 30 cases of congenital tuberculosis, found that in 14 the lymph nodes of the lung were involved alone or predominantly, and in 13 the lymph nodes of the liver predominantly, suggesting a primary complex of the lung or liver respectively

Bertoye (1936) amongst others suggests that the liver is often the site of the primary complex because it is the first organ to come into contact with infected blood; he adds that in cases of primary infection of the liver and lungs simultaneously the sites are determined by the fact that each organ has a sluggish circulation. Most authors have been content to accept this explanation, but it does not explain why no primary complex has ever been described in any organ other than the liver or lung.

Most of the blood returning along the umbilical vein is shunted past the liver by way of the ductus venosus, and this fact, combined with the knowledge that foetal tuberculous bacillaemia occurs, makes it likely that all the foetal organs come into contact with *Myco. tuberculosis*. Further, Brickner (1927) has shown that the arrest of particulate matter is best achieved by the liver, spleen, bone marrow and lungs and next best by the renal cortex and adrenal, while Rich and McCordock (1929) state that experimentally *Myco. tuberculosis* behaves in a manner similar to particulate matter when injected intravenously. It would appear likely, therefore, that following haematogenous spread, the foetal organs are infected with *Myco. tuberculosis* in proportion to their ability to remove circulating organisms from the blood stream. Subsequently, other factors must operate to achieve the disease pattern observed whenever a primary complex has been described. The following explanation is offered.

It can be shown experimentally in animals that after haematogenous spread infection with *Myco. tuberculosis* some clumps of organisms multiply and form a lesion, while others are killed and absorbed (Rich and Follis, 1942). This appears to be due to the varying abilities of different tissues to support the growth of the organism. It seems probable that the mechanism must be similar in congenital tuberculosis, and it is suggested that the infecting organism usually dies out in all the organs except the liver and sometimes the lung. Siegel (1934) states that the lung and not the liver is the organ most often infected, but he does not distinguish between primary and miliary lesions, a point of obvious importance.

It is interesting to speculate why primary liver infection occurs in the foetus, in view of the rarity of progressive tuberculosis (other than miliary) in the adult liver. Thus Ashton (1946) was able to find in the literature of the 10 years before publication of his paper, only one example other than his own of massive tuberculosis of the liver.

The importance of adequate oxygen supply to the growing *Myco. tuberculosis* has been stressed

by a number of workers, such as Rich and Follis (1942). Since the foetal liver receives blood direct from the umbilical vein before it has mixed with the blood of the inferior vena cava, the oxygen tension in the blood supplying it must be high compared with that of the rest of the foetal body, the opposite of what is found in the adult. Rich (1946) has suggested that in cases of primary infection of the liver and lungs at birth the lesions in the lungs develop more rapidly than those in the liver, because the former are exposed to a higher oxygen tension; thus at the time of death the two lesions are equal in size whereas at birth the liver complex exceeded that of the lung. Following primary infection, the regional nodes become invaded by *Myco. tuberculosis*. The terminal miliary spread, which occurs in nearly all cases, probably originates from these nodes which infect the blood stream, either directly or by way of the thoracic duct.

LYMPHATIC SPREAD. Since the placenta is embryologically part of the foetal body, it is possible that infection of that organ could act as a primary lesion. In that case the regional nodes in the porta hepatis would become involved (i.e. the first to be encountered along the path of the vein draining the part). The lymphatic drainage of the placenta does not appear to have been studied adequately, and no reliable data could be found on this subject; an attempt is being made to investigate the matter. Until more information is available the possibility of lymphatic spread along the umbilical cord must remain *sub judice*.

Summary

The literature concerning congenital tuberculosis is reviewed to date and the most recent cases evaluated, using the same criteria as Beitzke (1935) and Hughesdon (1946). A new case is put on record, and the pathogenesis of the condition is discussed in detail.

I should like to thank Mr. Riddell for permission to publish details of a case under his care. I am grateful to Dr. Wordley for his help and encouragement; to Dr. Mason for clinical data; and to Dr. Thomas and Dr. Urich for help in the Spanish and German translations. Mr. Dallan kindly photographed the specimens.

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CLINICAL OBSERVATIONS ON PYLORIC STENOSIS IN PREMATURE INFANTS

BY

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Little attention has been given in the past to the incidence and clinical features of hypertrophic pyloric stenosis in premature infants. We have observed three cases of this disease in very premature infants within a period of 18 months in one of the premature nurseries in the Simpson Maternity Hospital, Edinburgh. These cases are of special interest because continuous clinical records from birth to convalescence are available. The literature contains a considerable number of brief references to pyloric stenosis in premature infants (Bloch, 1907; Steen, 1930; Donovan, 1932; Gallagher, 1937; Sheldon, 1938; Dobbs, 1939; Vickers and Conrad, 1940; Ford, Brown and McCreary, 1941; Levi, 1941; Williams, 1942; Todd, 1946; 1947; Laubscher and Smith, 1947; Josephs and Hendry, 1950), but no detailed clinical records such as these which illustrate the manner of development of the disease, and certain features which appear to be peculiar to premature infants.

The smallest premature infant whom we have observed to develop the disease weighed 3 lb. 3 oz. at birth; this infant will not be included in this paper, because the clinical record is less detailed than in the cases of those recorded.

Case Records

Case 1. Male: a binovular twin.

Mother's last menstrual period, first day ..	September 20, 1949
Expected date of delivery ..	June 27, 1950
Born	April 21, 1950
Birth weight	3 lb. 3¾ oz.
Foetal age at birth	30 weeks 3 days

Signs of pyloric stenosis began on the thirty-sixth day of life, that is at the foetal age of 35 weeks 4 days. Rammstedt's operation was performed at the foetal age of 36 weeks 4 days when the weight was 3 lb. 5½ oz.

The mother, who had mitral stenosis, developed pre-eclamptic toxaemia which necessitated the induction of labour during the thirty-first week of pregnancy. This was the second pregnancy; the first child was a girl. Male binovular twins were born spontaneously, the first being vertex L.O.A., and the second vertex R.O.A. The first, who weighed 3 lb. 3¾ oz., later developed signs of pyloric stenosis, but the second, who weighed 3 lb. 5½ oz., died at the age of 39 hours. The latter baby showed clinical signs of the effects of intrapartum anoxia, notably atelectasis: necropsy confirmed intrapartum anoxia with subsequent respiratory failure as the cause of death; examination of the stomach did not show any evidence of pyloric stenosis.

The progress of the surviving twin during the first eight weeks of life, covering the period of illness caused by the pyloric stenosis and the early stages of convalescence after Rammstedt's operation, is shown in Fig. 1.

A 'trufood' formula fortified with 'prosol' (62% protein) compound was begun on the third day. Feeding was by gavage. The baby's condition steadily improved and the weight, after declining to 3 lb. 1 oz. on the tenth day, rose steadily and equalled the birth weight on the thirteenth day. During the fourth week the weight slowly declined but the temperature, which hitherto had usually been very subnormal, began to attain a higher level, though it remained unstable. At the end of the fourth week the baby vomited once on each of three successive days, but there was no further vomiting during the fifth week during which the weight increased steadily with a gain of 7½ oz. Vomiting recurred at the beginning of the sixth week, on the thirty-sixth day, when one vomit occurred. On the next two days there were three and six vomits respectively, several being copious. The steady weight gain of the fifth week was continued up to the thirty-eighth day, the third day of vomiting. Persistent vomiting continued through the following four days, accompanied by a subnormal number of stools and a rapid loss of weight amounting to 9½ oz. On the first of these days coffee-ground vomitus was seen on two occasions; on the second, which was the fortieth day of life, excessive gastric peristalsis was seen, a small

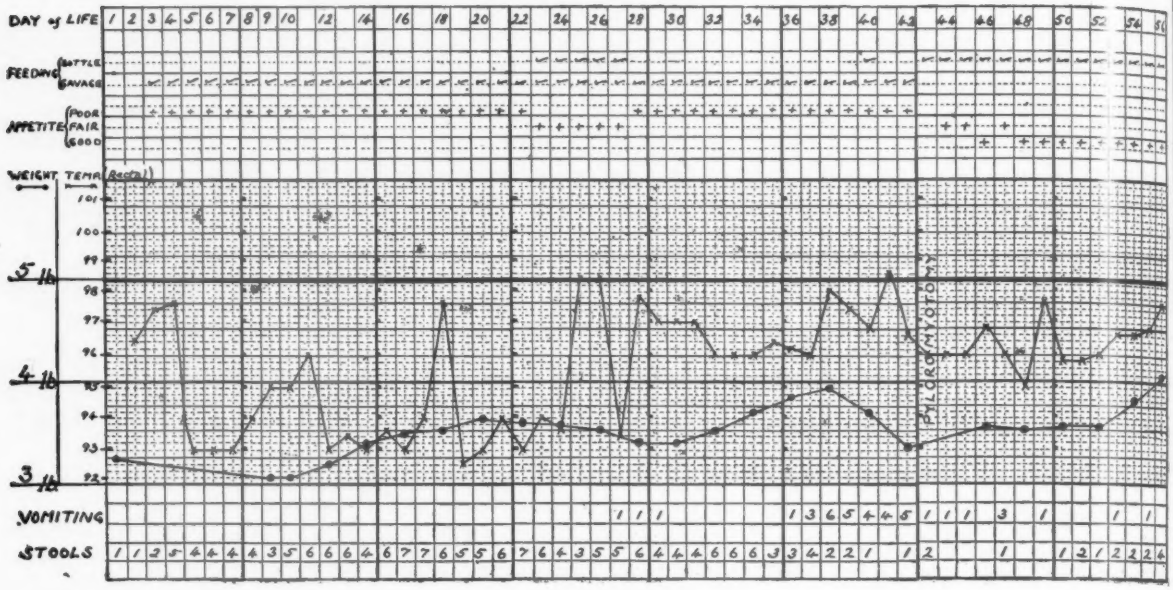

FIG. 1.—Clinical chart of Case 1 from birth until after recovery from pyloric stenosis.

pyloric tumour was felt and a diagnosis of pyloric stenosis made; and on the third projectile vomiting was first noted. On and after the third day of persistent vomiting fewer stools were passed. Occasional bottle feeds were given during most of the fourth week, but the appetite was so poor that bottle feeding was discontinued. It was again attempted on the day on which pyloric stenosis was diagnosed, but lack of appetite necessitated the resumption of gavage feeding which was continued up to the time of the operation on the forty-third day. The original 'trufood-prosol' formula was discontinued five days before the operation, and, after two days on glucose water, a regime of dilute sweetened condensed milk (Nestlé's) was instituted and continued up to the day of operation. During the three days between the diagnosis being made and the operation gastric lavage was carried out before some of the gavage feeds and saline hypodermoclyses with hyaluronidase were given to improve the baby's hydration and general condition.

Rammstedt's operation was performed by J.J.M.B. on the forty-third day of life. The weight was then 3 lb. 5½ oz. Cyclopropane and local anaesthesia were used. A small, hard pyloric tumour was found. After the operation Nestlé's milk was given in increasing strength and quantity for ten days when it was replaced by half-cream national dried milk. The appetite appeared to improve after the operation and all feeds were given by bottle; feeding was rather slow for the first three days but it was consistently good thereafter. A small vomit occurred once on each of the first three days of convalescence, and at less frequent intervals thereafter until a fortnight after the operation. Underfeeding accounted for the failure to gain weight and the infrequent stools until 10 days after the operation. A substantial increase of the diet at that stage was immediately followed by a rapid and steady gain in weight which continued until the infant was discharged from hospital at the age of 14½ weeks, when he weighed 7 lb. 2 oz.

Case 2. Male: single birth.

Mother's last menstrual period, first day ..	July 20, 1949
Expected date of delivery ..	April 27, 1950
Born	February 25, 1950
Birth weight	3 lb. 14½ oz.
Foetal age at birth	31 weeks 2 days

Signs of pyloric stenosis began on the tenth day of life, that is at the foetal age of 32 weeks 5 days. Rammstedt's operation was performed at the foetal age of 35 weeks 3 days when the weight was 3 lb. 2 oz.

The cause of the premature labour was not evident in this case. The birth was spontaneous, vertex L.O.A., and the infant's condition was fairly good. He was the first child. Progress during the first six weeks of life, covering the period of illness caused by the pyloric stenosis and the early stages of convalescence after Rammstedt's operation, is shown in Fig. 2.

A 'trufood' formula fortified with 'prosol' (62% protein) compound was begun on the second day. Progress was normal until the tenth day when the appetite deteriorated and feeding became slow. On the twelfth day the appetite improved, but the infant vomited twice. He continued to feed fairly well on the thirteenth day and there was no vomiting: the birth weight was regained on this day but no further weight gain occurred until after the operation. On the fourteenth day the appetite had become poor again and feeding slow, and vomiting occurred twice, the vomitus being copious on one occasion. On the fifteenth day feeding was slow

throughout, but there was no vomiting. On the following day the feeding continued to be slow and two large vomits occurred. The weight, which had been stationary for two days, began to fall and continued to do so up to the day of operation. On the seventeenth day the anorexia continued and the infant vomited five times, the amount being large on three occasions. On the eighteenth day there was no change so the 'trufood-prosol' formula was replaced by 6% glucose solution. Anorexia and vomiting continued and some gavage feeding was instituted on the twentieth day, Nestlé's milk, one part in seven parts of water, being substituted for the glucose solution. On the twenty-second day gavage feeding was discontinued because the appetite had improved, and diluted breast milk was substituted for Nestlé's milk. Pyrexia, with a temperature of 101° F., was not explained. The improved appetite continued during the next day and no vomiting occurred for the first time for more than a week. The pyrexia, though diminished, continued. The improvement in feeding was short-lived, for on the following day, when whole breast milk was begun, the anorexia returned and there was one large vomit. Feeding was poor on the next day and there were seven vomits. During the next day feeding improved, the majority of the feeds being taken fairly well, but vomiting continued though less persistently. The unexplained pyrexia which had persisted for four days had subsided. On the following day, the twenty-eighth day of life, the slight improvement in feeding and diminution of vomiting were maintained. Exaggerated gastric peristalsis was observed, a pyloric tumour felt, and a diagnosis of pyloric stenosis made. The vomiting, which had been present for 16 days, was never described as projectile, though this characteristic may have occurred. The weight had fallen 12½ oz. in the 13 days after it began to decline. The frequency of the stools had been subnormal for 12 days, there being none on two days.

On the twenty-ninth day of life, the day following the establishment of the diagnosis, a Rammstedt's operation was performed by J.J.M.B. The baby then weighed 3 lb. 2 oz. Cyclopropane and local anaesthesia were used. The pylorus was greatly enlarged. No further vomiting occurred after the operation, and the baby fed well from that time, on increasing amounts of glucose water on the day of operation, and on increasing amounts of breast milk thereafter. The weight rose 5 oz. in the first five days after the operation and 9 oz. in the following six days. The child continued to make good progress, and he weighed 6½ lb. when he was discharged from hospital at the age of 11 weeks. A right inguinal hernia was observed at the age of 10 weeks; this was operated on at the age of 6½ months. The infant then looked healthy.

Case 3. Male: single birth.

Mother's last menstrual period, first day ..	May 15, 1948
Expected date of delivery ..	February 22, 1949
Born	January 4, 1949
Birth weight	4 lb. 4 oz.
Foetal age at birth	33 weeks

Signs of pyloric stenosis began on the twenty-sixth day of life, that is at the foetal age of 36 weeks 5 days. Rammstedt's operation was performed at the foetal age of 38 weeks 4 days, when the weight was 3 lb. 11½ oz.

The mother was admitted to hospital with a revealed accidental haemorrhage and labour was induced surgically. The foetus was in the frank breech position and delivery was satisfactory, but the infant's condition was poor at birth. A very narrow head with a pronounced degree of dolichocephaly was observed. In the first 24 hours there were numerous transient attacks of respiratory failure with cyanosis, a common effect of the intrapartum anoxia so often produced in antepartum haemorrhage. This was the fifth child; the first four were all girls.

Progress during the first six weeks of life, covering the period of illness caused by the pyloric stenosis and the early stages of convalescence, is shown in Fig. 3.

Feeding was begun with diluted breast milk on the third day and continued with full breast milk on and after the fifth day. The appetite was poor in the early weeks, necessitating gavage feeding in the first week and partial gavage feeding in the second and third. The baby's condition steadily improved during the first week and had become fairly satisfactory by the end of it; the subnormal temperature persisted to the age of 2 weeks. The weight began to rise slowly on the tenth day, and

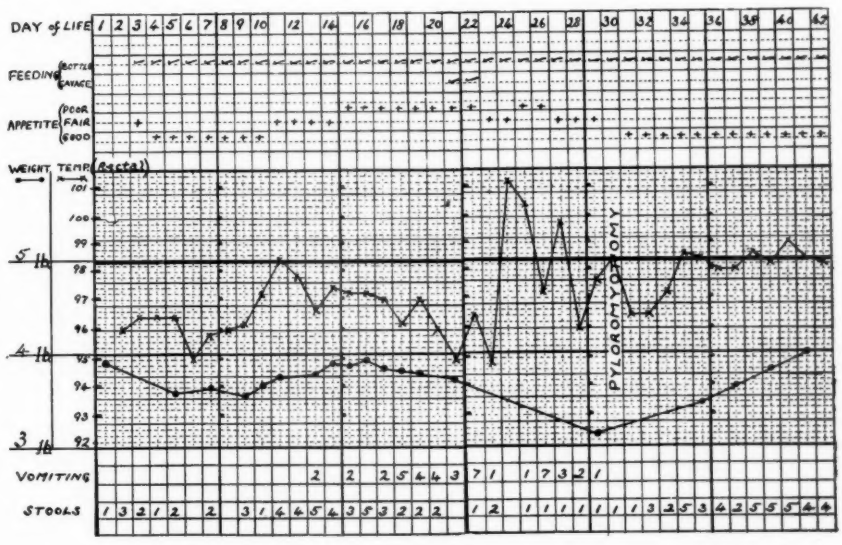

FIG. 2.—Clinical chart of Case 2 from birth until after recovery from pyloric stenosis.

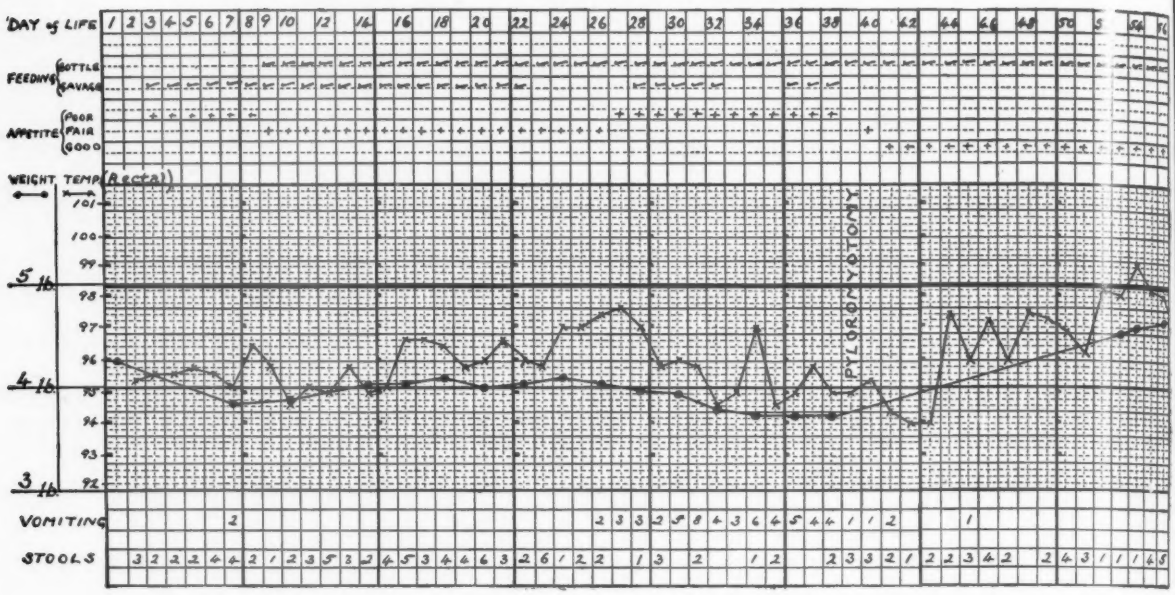

FIG. 3.—Clinical chart of Case 3 from birth until after recovery from pyloric stenosis.

the baby gained 3½ oz. in the following eight days. Bottle feeding alone was instituted at the age of 3 weeks but the appetite was not uniformly good and some feeds were taken slowly and remained unfinished. On the fourth day of bottle feeding, the twenty-sixth day of life, the appetite deteriorated and a phase of persistent vomiting, subnormal defaecation, and declining weight began. During the 13 days of this phase, until Rammstedt's operation was performed, the appetite remained poor, necessitating the resumption of partial gavage feeding on the third day. After five days of such feeding there was a slight improvement and gavage feeding was discontinued, but three days later partial gavage feeding was again necessary and was continued at some feeds to the time of the operation. Vomiting remained very persistent during the whole of this period, there being an average of four vomits per day and many were very copious. The bowels moved infrequently, sometimes at intervals of two or three days. The weight, which had remained stationary between the ages of 2½ and 3½ weeks and immediately before vomiting began, fell gradually during the first eight days of the vomiting phase, the loss being 6 oz., and it then remained stationary until after the operation five days later. The temperature receded to a subnormal level on the seventh day of the vomiting phase, and, except on a few occasions, remained depressed until after the operation. On the seventh day of the vomiting phase, at the age of 31 days, large waves of gastric peristalsis were observed, also 'slightly projectile' vomiting, but no pyloric tumour could be felt. The tumour was felt on the following day, however, and the provisional diagnosis of pyloric stenosis thus confirmed.

Six days after making the diagnosis Rammstedt's operation was performed by J.J.M.B., after preparation with gastric lavage and saline hypodermoclyses. Cyclopropane and local anaesthesia were used. The stomach was not grossly dilated or hypertrophied. The tumour was small and very hard. After the operation small hourly feeds of glucose water were given in increasing amounts until the second day when breast milk was resumed. The amount was gradually increased during the following days. The appetite had notably improved when feeding was resumed after the operation, and all feeds were taken well from the bottle thereafter. Slight vomiting occurred on the first two days after the operation, once on the first and twice on the second, and then ceased. The infant's general condition steadily improved and the subnormal temperature, which had been present for a week before the operation, resumed a normal level five days afterwards. The weight gained was 12½ oz. in the first two weeks after the operation, and it continued to rise steadily. He weighed 5 lb. 10 oz. when he was discharged from hospital at the age of 11 weeks.

It was realized at the age of 5½ weeks that the infant's inclination to lie in the frank breech position with adduction of the right leg, which had been noticed since birth, was attributable to congenital dislocation of the hip on the right side. Orthodox treatment was begun at the age of 9 months. As infancy progressed the eyes were noticed to move in a slow, nystagmoid manner, and the pupils not to react to light, and blindness was suspected. At the age of 1 year Dr. J. R. Paterson examined the eyes under general anaesthesia and reported that: 'Although the pupils remained large even in bright light, they contracted under the anaesthetic. Retinal examination showed gross congenital abnormality of both discs. These were much paler than normal, very poorly defined, and the vessels entered at their lateral sides. The child is blind and the condition not remediable.'

Discussion

Frequency of Pyloric Stenosis in Premature Infants. The scant attention given in the literature to the occurrence of pyloric stenosis in premature infants, and the tendency to consider it worthwhile to publish individual cases, suggest a lower incidence of the disease in premature than in full-term infants, but the available data on the subject do not justify such an assumption. Unfortunately, the proportion of premature infants has not been mentioned in most of the large series of cases of pyloric stenosis which have been published. In those series in which the proportion is given, the wide variation in the incidence is surprising; for instance, Levi (1941) had eight premature infants with a birth weight of 5½ lb. or less in his series of 100 cases, whereas Svensgaard (1935) had only three 'premature' infants of unknown birth weight in her series of 224 cases. Perusal of the records of 470 infants with pyloric stenosis who were admitted to the Royal Edinburgh Hospital for Sick Children in the last 15 years has not enabled us to determine the proportion of premature infants in the series, since accurate birth weights were available in only a minority of cases: 26 of the series (5·5%) were said to have weighed 5½ lb. or less at birth, but the birth weight can be regarded as reliable in only eight cases in which birth took place in hospital. Six of the 18 infants who were born at home were said to have had a birth weight of less than 5 lb.; five of them probably weighed less than 5½ lb., since the estimated gestation period was 35 weeks or less, but the sixth was estimated to be full time. The 12 remaining infants were said to have had a birth weight of 5 to 5½ lb., and it is probable that some of this group had a birth weight exceeding the standard for prematurity of 5½ lb. Although the above evidence is not of much value in helping to determine the relative incidence of pyloric stenosis in premature and mature infants, it suggests that there is probably no significant difference. The matter can be settled only by a careful follow-up of a very large number of consecutively born infants.

Clinical Features Peculiar to Premature Infants. The published cases do not give sufficiently detailed evidence to render such an assessment possible, but analysis of the detailed records in our three cases reveals certain features which appear to be peculiar to premature infants, particularly small premature infants. These features concern the appetite, the type of vomiting, and the significance of gastric peristalsis.

APPETITE. In all three cases the appetite, which had been fairly good after the initial anorexia normally found in very premature infants, showed pronounced deterioration when the signs of pyloric stenosis developed (Figs. 1, 2, 3). This feature probably occurs in the majority of very premature infants unless the disease develops at a later stage than in our three cases; it is probably uncommon in less premature infants who usually feed well in a manner reminiscent of the voracious appetite of the mature infant with pyloric stenosis.

TYPE OF VOMITING. The vomiting in our three cases was not notably projectile. Others have observed projectile vomiting in less premature infants. It seems probable, therefore, that this unreliable but suggestive sign of pyloric stenosis is unlikely to be of much diagnostic value in small premature infants.

SIGNIFICANCE OF GASTRIC PERISTALSIS. Fairly large waves of gastric peristalsis were observed in all our cases, but often they were no larger than the waves frequently seen through the thin abdominal wall of normal small premature infants. Vickers and Conrad (1940) saw no peristalsis in their case (birth weight 4 lb. 0 oz.), and Josephs and Hendry (1950) only 'weak peristaltic waves' in an infant whose birth weight was 4 lb. 6 oz. We believe that exaggerated gastric peristalsis is a much less useful sign of pyloric stenosis in premature than in mature infants.

Diagnosis in Premature Infants. The diagnosis of pyloric stenosis in small premature infants is more difficult than in larger infants, because of the absence of certain classical signs. The development of anorexia associated with vomiting usually suggests an infection, but the progressive accentuation of the vomiting, the steady loss of weight, and the development of constipation constitute a picture which should always suggest the possibility of pyloric stenosis in spite of persistent anorexia.

Palpation of the hypertrophic pylorus, which is easily felt through the thin abdominal wall of premature infants, is the only sure sign of pyloric stenosis. It was palpated without much difficulty in our three cases.

Treatment in Premature Infants. There is no doubt that pyloric stenosis in premature infants, however small, should be treated surgically without delay. The prerequisites of success are the same as in all cases of pyloric stenosis, notably adequate pre-operative water and electrolyte equilibration; a skilled paediatric anaesthetist; strict isolation and good paediatric nursing. In our cases there was a dramatic improvement of the appetite after operation and convalescence was very satisfactory (Figs. 1, 2, 3).

Prompt surgical treatment is particularly important in premature infants because of the serious effects of the prolonged malnutrition inevitably associated with medical treatment, and of the lack

of sustaining tissue reserves. Also there is a much greater risk of contracting infections, which are much more serious to premature infants, in conditions of prolonged malnutrition and hospitalization.

Aetiological Considerations. It is interesting to speculate on the possible aetiological significance of the relationship, if any, between the maturity and the age at which manifest pyloric stenosis develops. The age at which symptoms developed, in the 17 published cases in which this fact is given, did not bear any relationship to the degree of prematurity, and was no greater than the age at which the disease develops in mature infants. This fact appears to us to prove that post-natal processes, presumably increased activity of the musculature of the alimentary tract associated with the method of nourishing the organism inaugurated at birth, are responsible for the development of manifest pyloric stenosis, which rarely occurs before the age of 10 days, whatever the degree of maturity at birth. Since hypertrophy of the pyloric musculature is present in increasing degree for some time before clinical pyloric stenosis develops and has been observed at necropsy in stillborn infants, and since it may develop within two weeks of birth in very premature infants born two months before term, there would seem to be little doubt that (1) hypertrophy of the pyloric musculature is a congenital disorder, and (2) the further development of the condition to clinical pyloric stenosis is dependent on the operation of post-natal digestive processes in excess of a certain period, irrespective of the degree of maturity of the infant.

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CONGENITAL ANTERIOR ANGULATION OF THE TIBIA

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It is proposed in this paper to present two cases of congenital anterior angulation of the tibia. Surprisingly little mention is made in standard paediatric textbooks of this condition, which is probably more common than is generally believed. Further, speculation as to its cause may be of value at the present time when antenatal paediatrics is arousing such widespread interest and when prevention of certain congenital deformities is becoming more than a mere possibility.

The vast majority of cases of congenital anterior angulation of the tibia reported in the literature occurred in association with a congenital absence of the fibula.

The earliest reference to congenital anterior angulation of the tibia which it has been possible to trace is a report by Proudfoot in 1846 of a 'case of compound fracture of the tibia in utero and congenital talipes talus'. In all probability there was an associated fibular maldevelopment in this case. On reading the first two paragraphs of Proudfoot's article, which are worthy of quotation in full, one is not surprised that the erroneous diagnosis of intra-uterine fracture was made.

> 'Mrs. F., age 28 years, of sanguine temperament, and who has always enjoyed good health, during the sixth month of gestation, and of her third pregnancy, while attempting to pass through a very narrow passage, was severely pressed on the abdomen, and immediately experienced a violent pain in that region, accompanied with nausea and faintness. The following day she was threatened with abortion, having pain and some haemorrhage. These symptoms continued for some days, and occasionally reappeared in a light degree, up to the time of her delivery, which occurred at full time and was perfectly natural. At birth, the right foot of the child (a female) was found permanently extended and turned upward, pressing against the side of the leg, above the external malleolus.
>
> The tibia of the same side, about the middle of the bone, had apparently been the seat of a compound fracture; the two ends had united, at a slight angle anteriorly, and opposite to this angle there was a cicatrix, evidently of some time standing; there was considerable thickening of the parts near the seat of injury.'

In 1898 Cotton and Chute had gathered together and analysed no fewer than 128 cases of congenital absence of the fibula. The number of published case reports appearing thereafter in the literature may be gauged from the fact that Lapasset and Cahuzac in 1935 had found records of 295 cases of congenital absence of the fibula.

Kirmisson (1898) gave a full clinical description of congenital absence of the fibula in his textbook, adding six cases of his own to the literature, which he reviewed. Complete absence of the fibula was more common than partial absence and the condition was more often unilateral than bilateral. Anterior angulation of the tibia at the junction of its upper two-thirds and lower third was a usual association. The summit of the angle commonly pointed inwards and this, together with retraction of the tendo Achillis, resulted in an equino-valgus position of the foot. Overlying the angle, a 'scar' was constantly found. Absence of one or more toes with the corresponding metatarsals was common, usually those of the lateral side of the foot. The whole limb was atrophied to some extent. Other malformations of the affected limb were not rare; shortening of the thigh, dislocation of the hip and genu valgum. Congenital deformities elsewhere in the body had also been associated, such as cleft palate and complete or partial absence of the radius.

Discussing the pathogenesis, Kirmisson argued convincingly against the condition being caused by intra-uterine fractures, under which heading these cases had previously been described. He thought the most tenable theory was that which supposed a mechanical cause operating during the first two months of pregnancy, the result of pressure exerted by a small amniotic sac, often combined with the effect of amniotic adhesions. He thought these adhesions were also responsible for the scars.

Kirmisson also noted the existence of cases of angulation of the tibia but with an otherwise normal skeleton. In some of these, intra-uterine fracture was a possibility as a pseudarthrosis was present at the point of angulation, but he did not think this a reason for rejecting the pressure theory. The prognosis depended on the amount of atrophy of the limb.

Potel (1925) gave a more detailed description of cases in which both tibia and fibula were present. He did not believe the theory of amniotic compression, but thought the deformities were due to a lesion of the mesoderm during its differentiation. The bending was attributed to the lengthening bone being restrained by a lesser development of the surrounding muscle mass. The scar was simply due to stretching of the skin, or perhaps to amniotic adhesions in some cases.

In his studies on pre-natal lesions of striated muscle as a cause of congenital deformity, Middleton (1932, 1934) published three further cases of congenital angulation of the tibia, one of which was associated with radiological absence of the fibula. He preferred the term 'congenital tibial kyphosis'. In an attempt to explain the associated talipes equinus which was apparently produced and maintained by the short calf muscles, Middleton relegated the bony angulation to a secondary place and viewed the muscular shortening as the primary factor. He supposed that there was a relative failure during intra-uterine life of the last stage of growth (i.e. growth in length) of the developing myocyte, leading to a progressive retraction of the tendo calcaneus, and hence to the production of an equinus deformity at the ankle joint. When the ankle joint had become plantarflexed to its fullest extent, the process of relative shortening continuing, the strain fell upon the young shaft of the tibia, which being still cartilaginous, naturally bent at its weakest point which is the junction of the middle and distal thirds. With the advent of full ossification of the diaphysis of the tibia the process of progressive deformity came to an end. The dimples were said to mark the spots where bursae were likely to develop in later life.

Browne (1936) put forward strong arguments in favour of a mechanical origin for many congenital deformities, including 'fracture of the tibia'. He suggested that this was due to the effects of normal mechanical and hydraulic pressure in association with faulty development of the bones, the weaker leg being bent over the other. He thought that skin dimples also were the result of pressure and occurred over bony points in contact with the uterine wall.

Freund (1936) pointed out that most of the reported cases of congenital absence of the fibula occurred in young children who may show total absence of the fibula on clinical and radiological examination, but a few years later present a rudimentary fibula in the radiograph. He believed that the diagnosis of congenital absence of the fibula should not be made before the fifth year of life at the earliest.

Chapple and Davidson (1941) had their interest aroused in the subject of the relationship between foetal position and certain congenital deformities by a male infant who was born with marked lateral bowing of both femora, laterally dislocated hips, shallow acetabula, but a skeleton otherwise normal. When the infant was folded so that each foot opposed the apex of the lateral curvature of the other thigh, drawing the legs up tailor-fashion, with each leg meeting the opposite femur at a right angle, it was found that the baby preferred this position which they termed 'the position of comfort'. They stressed the importance of determining the position of comfort as a routine part of the examination of newborn infants, both as a means of anticipation and prevention of bone and joint abnormalities and as an aid to the interpretation of existing deformities.

Williams (1943) added a further two cases of congenital angulation of the tibia to the literature, the first patient survived only 30 minutes and showed normal fibulae. The second revealed radiological absence of the fibulae and, after amputation had proved necessary, the distal portions of the limbs were dissected. There was a solid, strong fibular shaft of fibro-cartilage with absence of ossification and great predominance of the fibrous element. Histological examination of one of the skin dimples showed that only the elastic tissue was slightly deficient and that the deep layers of the true dermis were in immediate apposition to the periosteum over the bony cortex. Williams still adhered to the theory of a basic mesenchymal defect. This resulted in a limitation of muscle growth, producing the angulation, and a failure of transitional differentiation to fibro-cartilage, cartilage and true bone, causing the frequently associated defects. He stated that treatment was difficult and the functional outlook poor.

In a paper entitled 'Prenatal Bowing and Thickening of Tubular Bones with Multiple Cutaneous Dimples in Arms and Legs', Caffey (1947) published three cases in which there was symmetrical lateral bowing of the femora and symmetrical posterior bowing of the humeri. Distal to the knees and elbows there were similar, but usually unpaired, deformities of the tibiae,

radii and ulnae. The fibulae were present in all his cases. Large symmetrically-placed dimples overlay the salient angle in several of the deformed bones of his first two cases. At the level of the bone angulation there was shown radiologically a combination of cortical thickening on the concavity with cortical thinning on the convexity, with reduction in the calibre of the medullary cavity.

Caffey explained the cortical hypertrophy as being due to failure of absorption from within, and not as representing subperiosteal accretion on the external surface. Clinically there was a gradual post-natal regression of the bowing of the bones, especially in the upper limbs, and the cortical thickening tended to lessen. Two of Caffey's cases showed metaphyseal spurs on the medial aspects of the opposing bones at the knees, and he emphasized the similarity to Blount's disease. He particularly drew attention to the occurrence of co-existing symmetrical bowing of the bones of the arms in these cases.

Caffey produced some convincing evidence that the skeletal deformities could be explained satisfactorily in large part by assuming that there had been mechanical pressure operating on ectopic foetal extremities. The deviation from the normal foetal position needed to be only slight. He imagined the foetus packed in a cross-leg and cross-arm position, in which each foot pressed on the internal aspect of the opposite thigh, and each hand on the flexor surface of the opposite upper arm. The bone bowed at the site of impact and the skin caught between the summit of the curve and the uterine wall, underwent pressure atrophy which produced a dimple. Caffey considered that Middleton's hypothesis did not fit his cases as there was no evidence of muscle shortening, though he did not rule out the possibility that transient muscle shortening of early foetal life could produce persistent curvature of bone.

Recently Duraiswami (1950) has induced various skeletal abnormalities in the developing chick embryo by the use of insulin. One of his radiographs of a 3-week-old chicken shows ' pathological fractures ' of both tibiae with marked buttressing of the concavities of the bowed bones by subperiosteal new bone, insulin having been injected into the egg on the fourth day. Duraiswami was of the opinion that these skeletal deformities were due to an unchecked insulin hypoglycaemia acting on the embryonic cells during the early days of incubation.

Case Reports

Case 1. R.J., a full-term girl, weighing 8 lb. 14 oz., was born in Hillingdon Hospital on September 14, 1950. The mother was 39 years old and had had three normal children. There was no history of maternal illness during the first three months of pregnancy. At the 29th week of pregnancy a radiograph of the mother's abdomen was taken because it was thought to be unduly large, and twins were suspected: this revealed bilateral angulation of the humeri, femora, tibiae and fibulae of the foetus. In this projection no angulation of the radii and ulnae could be seen. Delivery was normal but the infant was asphyxiated and died 15 hours later.

The limbs showed bilateral talipes equinus and anterior bowing of the lower legs. There was a cutaneous dimple over the site of angulation on the anterior surface of each leg. Palpation revealed that the dimple overlay a bony prominence on the anterior border of the tibia. Similar dimples overlying bony prominences were present on each forearm.

Radiography (Dr. S. A. Maddocks) showed slight cortical thickening posteromedially in the femora and angulation of each tibia at the junction of its upper two-thirds and lower third, while the point of fibular angulation was slightly more proximal. Both tibiae and fibulae showed posterior cortical thickening. Each arm (Fig. 1) showed bony projections on the radius and ulna at the site of a mild angulation, with lateral cortical thickening on the right side. In this projection no angulation of the humerus was evident.

FIG. 1.—Radiograph (Case 1) of right arm, showing bony projections on the radius and ulna at the site of a mild angulation.

A post-mortem examination was carried out by Dr. W. H. A. Picton. One tibia and fibula (Fig. 2) were removed, and a radiograph of the specimen clearly demonstrated the bony architecture, with thinning of the cortex on the convex surface and thickening on the concave side (Fig. 3). The necropsy produced evidence that the baby died of asphyxia: both lungs were atelectatic and the brain showed subarachnoid haemorrhages and an area of small haemorrhages in the posterior part of the left internal capsule.

Case 2. M.W., a boy, was first seen at Hillingdon Hospital at the age of 5 months on January 8, 1951, when he was admitted because of collapse of the right upper lobe of the lung. The mother was a primipara aged 28 years. During the pregnancy she had no illness but her friends had remarked on the smallness of her abdomen and she had been able to wear and button up her ordinary coat until term. A normal

delivery occurred at full term, the birth weight being 6 lb. 7 oz.

When the infant was examined several deformities were evident. Both legs were bowed anteriorly and slightly laterally, more so on the right side, and the feet were in a mild equinus position, dorsiflexion being limited to 90°. Each leg showed a pair of cutaneous dimples lying anteriorly at approximately the same level just below the mid-point of the shin, and much deeper on the right side. Beneath the two dimples on each leg were prominences of the anterior borders of the tibia and fibula respectively. A shallow dimple overlay the head of the fifth metatarsal on each side.

FIG. 2.—Post-mortem specimen (Case 1) showing tibia and fibula.

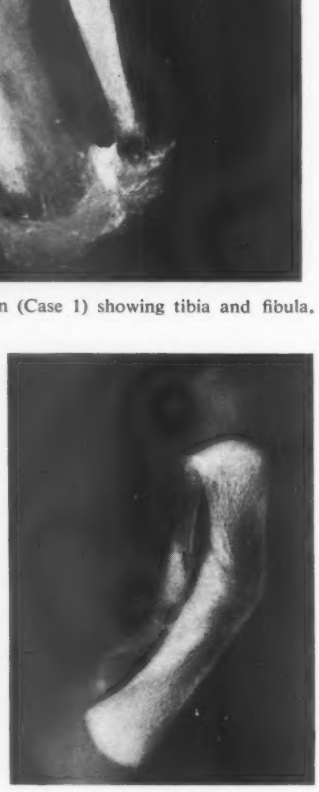

FIG. 3.—Radiograph (Case 1) of tibia and fibula after post-mortem dissection, showing angulation and bony architecture.

The dimples over the external epicondyles of the humeri and the olecranon processes were more marked than normal. The medial three fingers of both hands were fixed in flexion at the metacarpo-phalangeal and proximal interphalangeal joints, the little finger being the most severely affected. The chest showed a marked pigeon-breast deformity and bilateral triangular grooves into which the elbows and forearms fitted when pressed to the sides. The skull was plagiocephalic, the forehead being prominent on the right side. Micrognathia was a marked feature and there was a cleft of the soft palate.

FIG. 4.—Radiograph (Case 2) of right tibia and fibula at the age of 1 year, showing anterior angulation.

Radiography showed very slight lateral bowing of the femora, and the point of maximal bending of the tibia on both sides was just below the mid-point of the bone, and was associated with cortical thickening posteriorly: the anterior prominence was more marked in the fibula than in the tibia (Fig. 4). The left humerus showed mild posterior bowing in its lower half in a lateral view. The skull and spine were normal.

Attempts were made to reconstruct the foetal position of the legs. It was found that they could be folded up easily over the lower abdomen, so that each foot rested against the opposite thigh, without causing any distress to the infant (Fig. 5).

Manipulation and splinting of the fingers have shown an excellent result. After strapping the feet in the early months under the care of Mr. Eyre-Brook, regular manipulatory moulding of the lower legs and feet has been carried out for eight months with a slight improvement in the faulty alignment.

Discussion

It will be seen from the foregoing accounts in the literature that the condition of congenital angulation of the tibia with ossified fibulae is merely a *forme fruste* of the more severe and crippling deformity usually produced by congenital absence of the fibula. It has been shown that radiological absence of the fibula may merely indicate delay in ossification of the bone which is still present in cartilaginous or fibrous form.

Before considering some of the many theories put forward to explain the deformities found in this condition, Potel's (1925) words may be quoted: 'Que le péroné existe ou non, la coudure tibiale ne saurait avoir deux mécanismes différents et ces

affections sont absolument superposables et peuvent s'expliquer par un mécanisme identique '.

Although clinically angulation of the tibia may be the presenting feature, it must also be remembered that it may be only one manifestation of a pathology

FIG. 5.—Case 2 at the age of 5 months, showing attempt at reconstruction of foetal position.

affecting to a varying degree the long bones of both arms and legs. This has been emphasized by Caffey and is well shown by our first case. Any theory as to aetiology must take this fact into consideration.

The following theories must be considered.

Union of an Intra-uterine Fracture. The frequent occurrence of the angulation of the tibia as a bilateral and almost symmetrical deformity by itself renders this theory unlikely, as does the frequent presence of other associated defects. Examination of the bones at the site of angulation does not reveal any sign of a pre-existing fracture either radiologically or pathologically, although this does not preclude the possibility of fracture having occurred very early in foetal life.

Heredity. This does not appear to be an important factor. In only a few cases has a familial tendency been recorded: in most the condition appears unexpectedly in otherwise healthy stock.

Intra-uterine Failure of Growth in Length of Developing Muscle Unit. This theory as put forward by Middleton (1932, 1934) has already been described. One of the objections to it is that cases have been described without talipes, while in our second case only a mild talipes was present: if the shortening of the calf muscles was sufficient to cause bowing of the tibia, an extreme degree of talipes equinus would be expected. The theory offers no satisfactory explanation for the presence of the dimples.

Excessive Intra-uterine Pressure. This conception is not modern but fell into disrepute until recent years when attention was again drawn to it. That excessive intra-uterine packing can cause foetal deformities is an attractive theory which can explain most of the facts. Ideas as to the precise mechanism of the process are vague, but it seems not unreasonable to suppose that in certain cases the growth of the surrounding tissues fails to keep pace with that of the foetus in the amniotic cavity. If this difference in growth is considerable and occurs in the early weeks of pregnancy while the foetal bones are still cartilaginous, impairment of the vascular supply to the lateral side of the legs and feet, with consequent defect of fibular growth and absence of the lateral toes, might result. At the same stage, lesser degrees of packing might produce bending of the long bones only. On the other hand, pressure of any degree occurring somewhat later in pregnancy could produce bending of already ossifying long bones. Such ' pressure ' occurring early in pregnancy may be only transient. As Gaenslen (1915) has said, the original deficiency of amniotic fluid may be more than made up later in pregnancy. Our first case, if a result of pressure, would be an example of this. The mother's abdomen was thought to be unduly large when she came under observation, but at that time the deformities had already developed. Thus the absence of a small abdomen in the later months does not necessarily exclude mechanical pressure as a cause of foetal deformities. The size of a mother's abdomen throughout pregnancy, however, depends on so many factors that one should hesitate to ascribe too much significance to this observation in relation to foetal deformities.

The multiple deformities of our second case could be readily explained on the theory that increased pressure was exerted on the foetus from the early weeks onwards. Thus the tibial bowing would be due to pressure exerted through the long axis of the bone, the knee being in contact with the uterine wall and the foot pressed against the opposite thigh. The association of micrognathia and cleft palate has been attributed to acute flexion of the head on the chest which results in under-development of the mandible: the mouth does not provide ample space for the tongue and fusion of the palate is prevented (Chapple, 1950). Finally, stiff joints have been thought to be due to interference with the circulation by increased pressure (Browne, 1936): the fingers in our case would be flexed and pressed against the thorax.

Biochemical or Hormonal Influences. Reference has been made to the studies on the chick embryo by Duraiswami (1950). The production of

deformities of the tibia in some of the insulin-treated group is of great interest but it remains to be seen to what extent these findings apply to human embryology.

In order to throw more light on the aetiology of this condition, information about the conditions of pregnancy in further cases is needed. As suggested by Browne (1951), this study should include the mother's sensations during pregnancy, the size of her abdomen and the amount of amniotic fluid. In the baby, the distribution of deformities and dimples, and an attempt to determine the position of comfort are important. Enquiry should also be made about illnesses in early pregnancy which might come to have aetiological importance in relation to a lesion such as that envisaged by Middleton.

Summary

Two cases of congenital bilateral anterior angulation of the tibia with fully ossified fibulae are described. In the first case angulation of other long bones was present.

The more important papers in the literature are reviewed, most cases being described in association with congenital absence of the fibula.

Cases with congenital bowing or even angulation of the bones of the arms and legs may have tibial angulation as the only obvious clinical feature. The aetiology of the condition is discussed.

We wish to thank Dr. W. Arklay Steel for his advice in the management of the second patient, and we are grateful to Professor J. L. Henderson and Dr. C. G. Barnes for their many helpful suggestions.

The photographs are the work of Mr. E. Stride.

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CALCIFICATION OF THE LARYNGEAL AND TRACHEAL CARTILAGES ASSOCIATED WITH CONGENITAL STRIDOR IN AN INFANT

BY

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Calcification of the laryngeal and tracheal cartilages is not seen before the fifteenth year except in the body and greater horns of the hyoid, where it is present from the fifth month of prenatal life (Caffey, 1950). A search of the literature has not disclosed any description of this condition occurring in infancy, nor has it ever been seen in this hospital where over 7,500 chest radiographs are taken annually. For this reason the following case history was thought to be worth recording.

Case Report

The baby, a boy now aged 9 months, was born at full term by a normal delivery. He is the second child of healthy parents, and his sister, aged 21 months, is also well. There have been neither miscarriages nor still-births. He had a stridor at birth, and this has persisted

FIG. 1.—Antero-posterior radiograph showing the calcification.

FIG. 2.—A lateral radiograph of the same site.

unchanged. He has never been cyanosed or distressed, but has had severe recurrent upper respiratory infections from the first few days of life. He has, however, thrived well and can sit and stand at nine months. He has received cod liver oil from birth, but never in excessive amounts.

On examination, he was found to be a well-nourished child with a marked inspiratory stridor. There were generalized coarse râles in the chest, and minimal rib recession. There were no other abnormal findings, and no undue rigidity of the larynx or trachea was felt. A radiograph of the larynx and trachea showed calcification of the anterior parts of the hyoid, thyroid, cricoid and tracheal cartilages.

Radiographs of the whole skeleton showed normal bone structure, and there were no calcium deposits in the kidneys or the cartilages of the ears and nose.

The parents and sister were also radiographed but were found to be normal.

The blood chemistry was investigated and the following figures obtained: serum calcium 9·0 mg. %; blood inorganic phosphorus 3·7 mg. %; alkaline serum phosphatase 13·2 units (normal 10-20); plasma chlorides 606 mg. %; plasma bicarbonate 58·6 vols. CO_2%; blood urea 23 mg. %.

Laryngoscopy was performed by Mr. J. Crooks, who found the larynx and trachea to be normal in size and elasticity. The former showed marked infantile characteristics.

It was possible, therefore, to exclude hypervitaminosis D or a general metabolic disorder, as a cause of the atopic calcification, but no alternative aetiology was suggested. There seemed to be no direct association between the calcification and the congenital stridor.

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FACTORS INFLUENCING LACTATION

PART I. MATERNAL

BY

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Numerous factors have been reported to influence lactation. The role they play is hard to assess, and is generally based on either clinical impressions or inclusive evidence. Views on the importance of certain factors are conflicting, and from time to time a different factor is regarded as the most significant. Thus in the past different remedies have been advocated for difficulties in breast feeding though without any great success, beyond the stimulation of the medical and nursing profession to take more interest and care in helping women over their breast feeding difficulties. It would therefore seem desirable to assess more accurately the significance of various maternal factors which are reputed to impair lactation. The maternal factors which have been studied are age, parity, height, weight and health in pregnancy.

Material and Methods

Separate investigations were made of the effect of age, parity and pre-eclamptic toxaemia upon the duration of breast feeding. The women selected were those delivered in the Simpson Memorial Maternity Pavilion, Edinburgh, during 1948 and 1949. Two further groups of women, selected for studies on the possible relationship of height and weight to successful lactation, were chosen from women who were treated in the same hospital, but between January, 1947, and June, 1950. In all the investigations except that upon pre-eclamptic toxaemia every woman had given birth to a mature live infant. Women with twins were not investigated. Women with premature infants as well as mature infants were studied in the investigation on pre-eclamptic mothers. In each group every mother who fulfilled the conditions and fell within the limits of the investigation was included. The control groups of women who were compared with the groups under investigation were selected from women treated in the Simpson Memorial Maternity Pavilion during the periods of the investigations; these women, however, were selected at random, a similar number being chosen from every 1,000 consecutive admissions to hospital. The control groups were made comparable with the special groups by selecting mothers with either mature or mature and premature infants. Moreover, women with twins were excluded.

In the investigations relating to age, parity and pre-eclamptic toxaemia, two points were established; the first was the incidence of breast feeding, partial breast feeding and artificial feeding among the selected group of women at the time they left hospital. This was almost invariably the tenth day of the puerperium. If, as occasionally happened the mother stayed in hospital for more than two weeks after parturition, the method of infant feeding in use on the fourteenth day of the puerperium was recorded. The second was the effect of the factor under investigation upon the duration of breast feeding. This was established by following up for six months every woman with that factor who was entirely breast feeding her infant when she left hospital. The number and percentage of these women who were breast feeding for one, two, three, four, five and six months were calculated and recorded. Women who belonged to the group but who were giving their infants complementary feeds when they left hospital were similarly investigated.

In the investigation concerning women's height and weight both the mother and the infant were weighed at the hospital welfare clinic in the third or fourth week after the birth of the infant. They

were re-weighed each time the mother brought the infant for re-examination at the clinic, which was usually once a week. A record of the mother's weights was kept as well as her age and height. A note was also made of the mother's weight before she was pregnant. The infant's weights and method of feeding were recorded. From the data, both the mother's height and weight was correlated with the duration of breast feeding. The mother's weight was also correlated with the infant's weight progress provided the infant was breast fed.

Age

Studies on the influence of age upon lactation have shown that older women tend to have a lower milk yield during the first week of lactation (König, 1939; Ström, 1947; Waller, 1950) and more often stop breast feeding prematurely than do younger women (Woodbury, 1925; Stewart and Pratt, 1941). Robinson (1942), Norval (1947) and Herlitz (1946) confirmed this and considered that the reduction in the incidence of breast feeding occurred after women reached the age of 30. On the other hand Friedländer (1917), Bendix (1928) and Broman, Dahlberg and Lichtenstein (1942), considered that elderly women breast fed their infants longer than younger women. According to Herlitz (1946) and Douglas (1950), the different incidence of breast feeding in the two age groups was not statistically significant. Herlitz (1946) believed that the possible difficulty in breast feeding amongst older women was due to a relatively lower milk yield, but that this difficulty was minimized by the fact that a larger proportion of elderly women are multipara with a greater knowledge of breast feeding and a greater desire to breast feed their infants than younger women.

In this investigation the influence of age upon lactation has been ascertained by determining the percentage of both young and old mothers breast feeding their infants. The investigation involved two groups, primiparae and multiparae. In the first a group of 1,120 primiparae under 35 (young) was compared with a group of 135 primiparae over 35 (old). The percentage of women fully breast feeding, partially breast feeding and artificially feeding in each of the two groups of women in the second week of the puerperium was determined and the results recorded in Table 1. The results show that the proportion of women who fail to breast feed their infants satisfactorily in the second week of lactation is at least 32% greater in the group of elderly primipara.

The same method of investigation was adopted to compare the incidence of lactation in a group of 655 multiparae under 40 (young) with that of a group of 114 multiparae over 40 (old). These results were also recorded in Table 1. Again the figures show that the greater percentage of elderly multiparae are unable to breast feed their infants adequately in the second week of the puerperium. Thus, when comparing the incidence of breast feeding among elderly mothers with that found among young mothers, it is apparent that a larger proportion of elderly mothers irrespective of whether they are multiparae or primiparae require to give complementary or completely artificial feeds to their infants.

TABLE 1

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN YOUNG AND OLD PRIMIPARA AND MULTIPARA IN THE SECOND WEEK OF THE PUERPERIUM

Group	No. of Cases	Percentage		
		Complete Breast Feeding	Partial Breast Feeding	Artificial Feeding
Young primipara	1,120	81	9	10
Old primipara	135	49	27	24
Young multipara	655	82	9	9
Old multipara	114	46	30	24

An investigation was also made into the duration of lactation among young and old mothers. Again primiparae were compared with primiparae and multiparae with multiparae. The ages dividing the young from the old were the same as in the first part of the investigation. For this purpose 145 young primiparae and 33 old primiparae, all of whom were breast feeding their infants completely and satisfactorily when they left hospital, were followed up. The number in each group that breast fed for one, two, three, four, five and six months was determined. From the results the percentage of women in each group who lactated for one, two, three, four, five and six months was calculated and recorded in Table 2. From this table it is apparent that the percentage of women continuing to breast feed from month to month was similar in the two groups.

The duration of lactation of 107 young multiparae and 550 old multiparae who were completely breast feeding their infants in the second week of the puerperium was investigated in a similar manner. The results have been recorded in Table 2. They show that the percentage of elderly multiparae who breast feed for one, two, three, four, five and six months respectively is similar to the percentage

TABLE 2

DURATION OF BREAST FEEDING OF 'YOUNG' AND 'OLD' PRIMIPARA AND MULTIPARA

Group	Age	Lactation in Hospital	No. of Cases	Percentage Lactating Each Month						
				½	1	2	3	4	5	6
Primipara	Young	Adequate	145	100	88	68	58	54	50	47
	Old	Adequate	154	100	98	69	60	54	50	47
Multipara	Young	Adequate	107	100	93	78	71	58	52	50
	Old	Adequate	114	100	93	79	71	59	52	52
Primipara	Young	Inadequate	130	100	49	23	17	12	11	11
	Old	Inadequate	19	100	37	16	16	10	10	5
Multipara	Young	Inadequate	51	100	34	17	14	9	7	6
	Old	Inadequate	18	100	22	6	6	0	0	0

of young multiparae lactating for those periods. It is therefore apparent that breast feeding at this stage of lactation is as satisfactory in elderly mothers as in young mothers, be they primiparae or multiparae.

A study has been made of the duration of breast feeding in young and old women who require to give their infants complementary feeds in the second week of the puerperium. The investigation was conducted along the same lines involving multiparae and primiparae who were completely breast feeding their infants when discharged from hospital. The percentage of both 130 young and 19 old primiparae and of a group of 51 young and a group of 18 old multiparae breast feeding for one, two, three, four, five and six months was determined and recorded in Table 2. The results obtained for young mothers did not differ appreciably from those obtained for old mothers. Thus evidence has been given to show that age does not influence a woman's ability to breast feed her infant after the second week of the puerperium.

The deductions drawn from the investigation into the possible relationship between age and lactation are: first, a higher proportion of older women, both multiparae and primiparae, have to give their infants complementary feeds during the second week of lactation and such mothers usually wean their infants soon after leaving hospital. Those who leave hospital fully breast feeding their infants continue to breast feed for as long as the control series of mothers. Secondly, a higher proportion of elderly women, both primiparae and multiparae, have to give artificial feeds to their infants before they leave hospital, which is usually on the tenth day of the puerperium. Thirdly, it is known that approximately 3% of all women leaving the Simpson Memorial Maternity Pavilion while these investigations were in progress were primiparae over 35 and 4% were multiparae over 40. It is therefore apparent that in only a very small proportion of the many women who wean their infants prematurely can weaning be attributed to the mother's age.

Parity

Reports on the influence of parity upon successful breast feeding vary. Peckham (1934), and Herlitz (1946) considered multiparae to be more successful in breast feeding than primiparae. This was probably due to multiparae being more experienced and physiologically better adapted to nurse (Herlitz, 1946), and to lactation in primiparae being more readily affected by ill health (König, 1939; Ström, 1947). It has been stated that close pregnancies may give rise to early weaning (Woodbury, 1925; Royal College of Obstetrics and Gynaecologists, 1948). More convincing evidence however has been given by Norval (1947), by Dykes (1949) and by Douglas (1950) to show that parity does not influence the duration of breast feeding.

To confirm or refute the general impression that parity did not influence a woman's ability to breast feed her infant the incidence and duration of lactation in multiparae and primiparae have been compared. The data used in the investigation into age and lactation have been re-examined. The incidence of breast feeding, partial breast feeding and artificial feeding amongst 1,255 primiparae was compared with that of 769 multiparae at the end of the second week of the puerperium. These women were of all ages and were selected at random from cases which were treated in hospital in 1948 and 1949. From Table 1 it is apparent that the incidence of breast feeding or partial breast feeding for primiparae does not differ appreciably from that for multiparae in the second week of lactation.

The duration of breast feeding of primiparae and of multiparae was also investigated. A group of 299 primiparae and one of 221 multiparae, comprising women who were entirely breast feeding when discharged from hospital, were followed up

for six months. The percentage of women in each group who breast fed their infants for one, two, three, four, five and six months was recorded in Table 2. The results indicated that the two groups of mothers were equally successful in breast feeding their infants for six months.

A similar investigation was made upon 149 primiparae and 69 multiparae who were giving their infants complementary feeds when they left hospital. The results given in Table 2 show that approximately the same percentage of women in the two groups breast feed their infants for six months.

Weight and Height

After childbirth many women are concerned about their weight because they consider they are too heavy or else because they are too light. Despite these complaints few studies of women's weight during lactation have been recorded. From those which are available it appears that the majority of women initially lose weight, on the average 2·30 kg. in the first 10 days and 0·68 kg. in the next 35 days (Stander and Pastore, 1940). They then gain weight until a month before or after their milk production has reached its maximum after which they again lose weight (Ylinen, 1937). Some women, however, steadily gain weight or lose weight (Ylinen, 1937). The older conception differed from this in that most women gained weight when they breast fed their infants (Schlossmann, 1905; Finkelstein, 1921; Laurentius, 1911; Peckham, 1934).

Both women's height and weight have been correlated with their milk yield or their ability to breast feed their infants. Wardlaw and Dart (1934) noted that undersized women tend to have lighter infants and smaller milk yields than taller women. Others have investigated the possible relationships of women's milk yield to body weight and failed to detect such a relationship (Macy, Hunscher, Donelson and Nims, 1930; Ylinen, 1937). Nevertheless, Ylinen (1937) considered that if a larger series of observations were made it might be possible to show that women who lost weight had on the average a better milk yield than mothers whose weight fluctuated or steadily rose. Observations made on women's nutrition and ability to breast feed their infants adequately have been made in countries where various degrees of under-feeding or starvation have existed. The results of these observations showed that undernourished women may have difficulty in breast feeding, some being able to breast feed their infants satisfactorily for a limited period while others never lactate adequately (Kütting, 1921; Kerpel-Fronius, 1947; Antonov, 1947; Dean, 1949). The different response to undernourishment was probably dependent on the type and degree of the dietetic deficiency, and evidence suggests that only grossly abnormal diets taken for a considerable period of time affect lactation adversely.

One investigation of the possible relationship of women's height, and two of the possible relationship of women's weight to their ability to lactate adequately have been made. That dealing with height was made to determine whether women under 5 ft. were as successful in breast feeding as taller women. To this end, a group of 123 women under 5 ft. and one of 1,487 women over 5 ft. were examined, and the number in each group who completely breast fed, partially breast fed and artificially fed their infants in the second week of lactation was determined. From these results the percentage of each group breast feeding, partially breast feeding and artificially feeding their infants was calculated and recorded in Table 3. The

TABLE 3

INCIDENCE OF DIFFERENT TYPES OF FEEDING IN WOMEN UNDER AND OVER 5 FT. IN THE SECOND WEEK OF THE PUERPERIUM

Group	No. of Cases	Percentage		
		Complete Breast Feeding	Partial Breast Feeding	Artificial Feeding
Over 5 ft. ..	1,487	79·5	10·2	10·3
Under 5 ft. ..	123	81·3	8·95	9·75

percentage obtained for the two groups was compared, and showed that women under 5 ft. were as successful in breast feeding in the second week of the puerperium as women over 5 ft.

The duration of breast feeding was studied in a group of 75 women who were under 5 ft. and a group of 280 women over 5 ft. All these women were entirely breast feeding their infants in the second week of the puerperium, and were followed up for six months. The number and percentage of women in each group who breast fed for one, two, three, four, five, and six months was ascertained. The percentage of each group who were breast feeding at each monthly stage is shown in Fig. 1, from which it is apparent that 53% of the women over 5 ft. breast feed their infants for six months while only 33% of women under 5 ft. breast feed for the same length of time. The difference is statistically significant. Thus, in this

investigation women under 5 ft. were not as successful in breast feeding their infants as the taller women. The degree of impairment in lactation noted in the small women, however, does not contribute to any great extent to the large number of prematurely weaned infants, because only 10% (approximately) of all women admitted to maternity wards are under 5 ft.

The possible relationship between the mother's weight in the third and fourth week of the puerperium and the duration of her lactation has been investigated. Two groups of women were used; one comprised 176 women who were below the average weight for their height and age, and the other comprised 207 women who were over the average weight for their height and age when they were weighed in the third or fourth week of the puerperium. All their weights, however, were within the range of normal for both non-pregnant or non-lactating women and the standards were those quoted by Werner (1942). Each woman was weighed on the same machine and all were followed up for six months. They all were completely breast feeding their infants when they left hospital. The number and percentage of each group of women who breast fed for one, two, three, four, five and six months was recorded in Table 4. The results suggest that the heavier group of women breast feed their infants on the average longer than the lighter group of women. The difference between the two groups is not statistically significant.

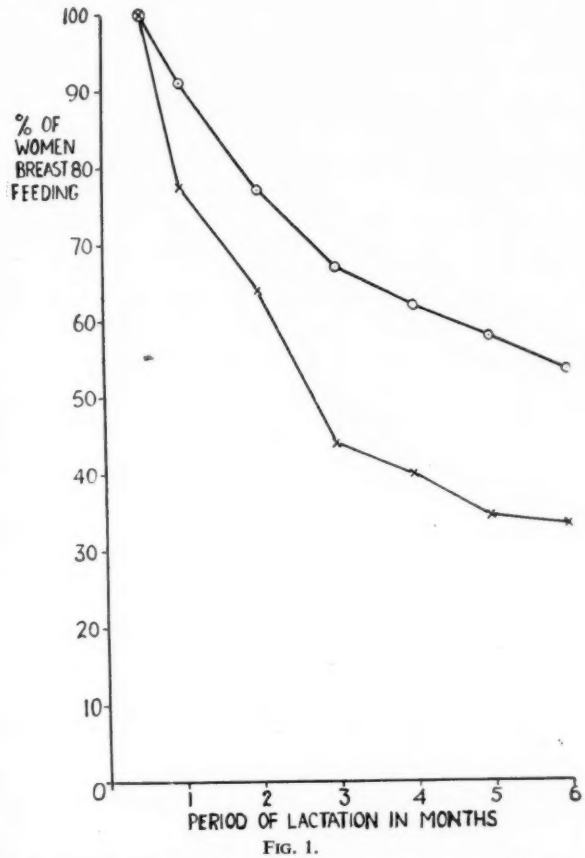

FIG. 1.

FIG. 1.—The duration of breast feeding among women who were both under (×) and over (⊙) 5 ft. tall.

It was not possible to follow up many women who were either below or above the normal weight for their age and height. Nevertheless the results obtained for six women who were below normal weight (underweight) and for 42 women who were above normal weight (overweight) in the third and fourth week of the puerperium deserve comment. The overweight women were investigated in the same way as were those described in the previous paragraph and the percentage breast feeding for six months (55%) recorded (Table 4). All the women were entirely breast feeding their infants when they left hospital in the second week of the puerperium. The results of this investigation indicated that the women who were overweight on the average breast fed for approximately the same period as women of average weight. The follow-up of the six women who were underweight showed that two of them breast fed for six months and in these cases the health of both the mother and infant was satisfactory. Thus some underweight women can breast feed their infants as satisfactorily as heavier women.

The second investigation into women's weights was made by comparing the weight progress of breast fed infants belonging to mothers whose weight increased during the first six months of

TABLE 4

WEIGHT IN THE THIRD AND FOURTH WEEK OF THE PUERPERIUM CORRELATED WITH THE DURATION OF LACTATION

Group	No. of Cases	Percentage Lactating Each Month						
		½	1	2	3	4	5	6
Overweight ..	42	100	86	79	71	64	60	55
Heavy	207	100	91	80	74	65	63	59
Light	176	100	84	74	61	52	51	50

TABLE 5

CORRELATION OF INFANT'S WEIGHT GAIN WITH MOTHER'S WEIGHT GAIN OR LOSS DURING FIRST 6 MONTHS OF LACTATION

Mother's Weight	No. of Cases	Average Weight of Infant (lb. oz.) at						
		Birth	4 wks.	8 wks.	12 wks.	16 wks.	20 wks.	26 wks.
Increased	89	7·9	8·12	10·6	12·1	13·9	14·13	16·6
Decreased	212	7·6	8·11	10·8	12·3	13·11	14·15	16·7

lactation with that of breast fed infants belonging to mothers whose weight decreased during the first six months of lactation. The women selected for the investigation were weighed in the third or fourth week of lactation and again at approximately the sixth month of lactation. The two values for each woman were compared; 212 lost from 1 to 23 lb., or an average of 9½ lb., during this time and 89 gained from 1 to 64 lb., or an average of 7⅓ lb. Many of these women were weighed frequently during the six months that they were under investigation and these cases almost always showed a constant rise or else a constant fall in weight. It was therefore apparent that fluctuation in both directions was unusual. The weight progress of the infants belonging to these mothers was recorded every week or every other week during the period of investigation. The infants were entirely breast fed until they were about 5 months old after which mixed feeding was gradually introduced in many cases. The average weight for each group of infants during the first six months of life was calculated from the results and recorded in Table 5. From inspection of Table 5 it is apparent that the difference between the two groups is not great. This might well occur by chance because the weight gain of infants varies greatly from case to case. Therefore, the variation in the mother's weight during lactation does not bear any relationship to her infant's weight progress as judged by the present series of observations on apparently healthy women. The investigation also revealed that 70% of mothers lose weight in the first six months of lactation while almost 30% gain weight throughout that period. Moreover, out of a series of 210 women in the first six months of lactation, 36% had returned to their pre-pregnant weight. The remaining women (64%) were still above their normal weight after lactating for six months. It appears, therefore, that both an increase or decrease in weight during lactation is a physiological process and that the change can be very marked without affecting either the mother's or infant's health and progress adversely.

Health in Pregnancy

Pregnant women are liable to the same diseases as the general public. Some diseases, such as acromegaly (Cameron, 1947) and the Arnold-Chiari syndrome, are associated with galactorrhoea (Ashkar, 1950), while others causing a systemic disturbance may impair a woman's chances of breast feeding her infant. It is stated that women with pyelitis (König, 1939; Robinson, 1942), nephritis and eclampsia during pregnancy (Peckham, 1933) are less likely to breast feed their infants than women who have been healthy during pregnancy. Whether pre-eclamptic toxaemia has a similar effect upon lactation is doubtful; Peckham (1933) and Brash (1948) state that the condition has on the average a deleterious effect upon lactation, but Robinson (1942) failed to confirm their conclusion. Disorders giving rise to no apparent systemic disturbance, as in the majority of cases of anaemia, albuminuria (Ström, 1947), lactosuria (Joslin, 1940) and enlargement of the thyroid gland without thyrotoxicosis (Robinson, 1942) do not affect lactation adversely. Owing to the difference of opinion on the effects of pre-eclamptic toxaemia upon lactation this problem has been investigated. No attempt, however, has been made to study the effects of other diseases that may occur in pregnancy because of the difficulty in obtaining a large enough series of women with a specific illness for such an investigation.

To this end a series of 292 women with pre-eclamptic toxaemia was investigated; 244 of these had mature infants and 48 had premature infants. They have been compared with two series of women who had not suffered from pre-eclamptic toxaemia; one comprised 3,058 women with either mature or premature infants and the other 1,899 women all of whom had mature infants. No mother in either series had twins. Every woman of both pre-eclamptic and control groups was examined during the second week of the puerperium and her method of feeding her infant noted under one of three headings, breast feeding, partial breast feeding and artificial feeding. The percentages of

pre-eclamptic women with mature infants in each group were then compared with the percentage of the control women with mature infants in each group. A similar comparison was made between pre-eclamptic women with mature and immature infants and the group of control women with mature and immature infants. The incidence of complete breast feeding, partial breast feeding and artificial feeding for each of these groups of women has been shown in Table 6. The figures indicate that in the groups with mature infants a greater percentage of pre-eclamptic women gave their infants complementary or artificial feeds than in the control series, there being 10% fewer pre-eclamptic women fully breast feeding their infants in the second week. When women with premature infants were included in the two groups the differences became more marked. This is partly due to the proportion of pre-eclamptic women with premature infants being greater than that of the control series with premature infants: 16% of premature infants amongst the offspring of pre-eclamptic women and 6% amongst those of the control series.

The duration of breast feeding has also been studied. In this analysis 115 pre-eclamptic women were followed up for six months after their confinement; 89 were entirely breast feeding, and 26 were partially breast feeding their infants when they left hospital. The number who breast fed for one, two, three, four, five and six months was determined and the percentage of women breast feeding each month calculated from these figures. The results are given in Fig. 2 with the results for a control series, which comprised 202 women who were fully breast feeding their infants and 143 partially breast feeding their infants when they left hospital. They were followed up and investigated in exactly the same way as was the group of pre-eclamptic women. No twins were included in the series. From Fig. 2 it is apparent that pre-eclamptic women who were entirely breast feeding their infants in the second week of the puerperium lactated as successfully as the control group of women, while the majority of both the pre-eclamptic women and the control group who left hospital giving complementary feeds very soon stopped breast feeding their infants. It is, therefore, apparent that if a pre-eclamptic woman is able to breast feed her infant adequately by the tenth day of the puerperium she is likely to be able to breast feed her infant for six months as any other woman with an adequate

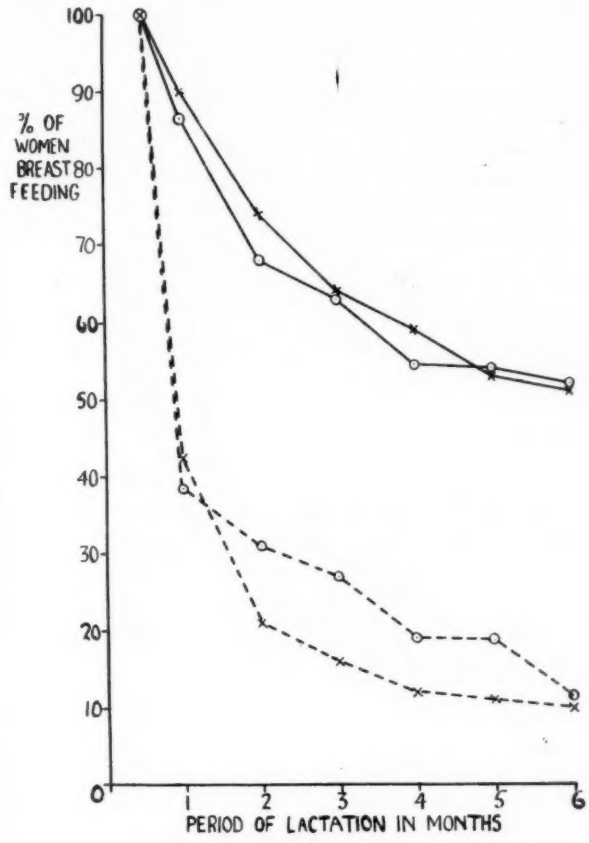

FIG. 2.

FIG. 2.—The duration of breast feeding among pre-eclamptic (⊙) and non-pre-eclamptic (×) women. Values are given for women in both groups who had adequate (—) and inadequate (– – –) lactation in the second week of the puerperium.

TABLE 6

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN PRE-ECLAMPTIC AND NON-PRE-ECLAMPTIC (CONTROL GROUP) MOTHERS IN THE SECOND WEEK OF THE PUERPERIUM

Group	Maturity of Infant	No. of Cases	Percentage		
			Completely Breast Feeding	Partially Breast Feeding	Artificially Feeding
Pre-eclamptic	Mature	244	69·7	13·5	16·8
Control	Mature	1,899	79·5	10·3	10·2
Pre-eclamptic	Mature and immature	292	59·6	12·3	28·1
Control	Mature and immature	3,058	76·6	9·9	13·4

supply of breast milk on the tenth day. They do, however, find greater difficulty in establishing adequate lactation during the first two weeks of the puerperium than do women who have not suffered from pre-eclamptic toxaemia. The percentage of women with impaired lactation attributable to pre-eclamptic toxaemia is small, for it is a fraction of the 7·5% who leave hospital with a history of pre-eclampsia during their pregnancy.

Conclusion

A series of investigations on the incidence and duration of breast feeding were made on women who were treated both as in-patients and as out-patients in the Simpson Memorial Maternity Pavilion, Edinburgh, between January, 1947, and June, 1950.

Elderly women more frequently gave complementary or artificial feeds to their infants than younger women in the first two weeks of the puerperium; those giving complementary feeds usually stopped breast feeding within a month of parturition, while those giving entirely breast feeds lactated adequately, in 50% of cases, for six months. This applied to both young and old mothers.

Women under 5 ft. more frequently weaned their infants prematurely than taller women. This difference was apparent after the second week of lactation and only between the third and twenty-sixth week of lactation.

Women whose weight was above the average for their age and height in the third and fourth week of the puerperium breast fed their infants as well as those whose weight was below average. A small group whose weight was below the minimum for their age and height had considerably more difficulty in breast feeding than heavier women. This latter observation may be of practical importance, and further observations into markedly underweight women would be of interest.

A study of women's weights between the third week and the twenty-sixth week after parturition showed that 70% of mothers who breast feed their infants for six months lost from 1 to 23 lb. in weight during that time. Thirty-six per cent. of all women who breast fed for six months had returned to their pre-pregnant weight by the end of that time. Almost 30% of women breast feeding for six months gained weight, their gain being 1 to 64 lb. The rise or fall in weight, even if marked, did not appear to affect the mother's health adversely. Nor did it appear to affect the infant's weight progress.

In the first two weeks of the puerperium more pre-eclamptic women required to give their infants complementary feeds and artificial feeds than did the control group; those giving complementary feeds usually failed to breast feed within a month of parturition, while 50% of those entirely breast feeding lactated adequately for six months. This applied to both the pre-eclamptic and control group of women. The greater difficulty in breast feeding in pre-eclamptic women was attributed partly to the mother's illness and partly to the higher incidence of prematurity in such women.

Impaired lactation due to age or small stature or pre-eclamptic toxaemia accounted for a very small proportion of women who prematurely wean their infants.

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PART II. PREMATURITY AND ABNORMAL LABOUR

The influence of prematurity and abnormal labour upon lactation has rarely been recorded in detail. It has been shown (Drillien, 1948) that women with premature infants breast feed less successfully than those with mature. Drillien also showed that the lower the birth weight of the infant the less likely it was to be breast fed. Of those cases which failed to establish lactation 60% were due to prematurity alone. Once feeding had been successfully established the commonest causes of subsequent failure in order of frequency were stated to be insufficient lactation (29%), prematurity (22%), illness of the mother (8·7%), difficulty in the infant fixing on the breast (7·8%) and breast abscess (3·9%).

The effects of complications of labour upon lactation have been studied by König (1939). He made an extensive investigation on women in hospital but only during the first two weeks of the puerperium. Women who lost large quantities of blood (over 1,000 ml.), or had forceps deliveries or Caesarean section were less successful in completely breast feeding their infants. In the case of forceps deliveries failure to breast feed was attributed (1) to a higher proportion of mothers developing endometritis, (2) the mother being older than the average, and (3) the babies having difficulty in feeding possibly because of the effects of birth injury. Herlitz (1946), who also studied the influence of forceps deliveries upon lactation, did not confirm König's conclusion. This may have been due to the small number of cases investigated (16). Since confirmation of Drillien's and König's work has not been noted in the literature it appears desirable to make further investigations into the effects of both prematurity and complications of labour upon lactation.

Prematurity

The incidence of breast feeding and partial breast feeding amongst women with premature infants was determined either at the end of the second week of the puerperium or earlier if the women were to leave hospital before that day. Two hundred and forty-eight mothers with premature infants were studied; none of them had twins. They were divided into groups according to the birth weight of their infants; one for those with infants weighing less than 4½ lb.; one for those with infants weighing 4 lb. 8 oz. to 4 lb. 15 oz. and one for those with infants weighing 5 lb. to 5 lb. 8 oz. A control series of 3,742 women who had mature infants was investigated in the same way. The incidence of breast feeding, partial breast feeding and artificial feeding in the three groups of mothers with premature infants and among mothers belonging to the control group has been given in Table 1. It is apparent from this table that the incidence of breast feeding among women with premature infants was less than among women with mature infants. There was a difference of 13% between the group of mothers with infants of birth weight of 5 lb. to 5½ lb. and the group of mothers with mature infants. The difference in incidence between women with premature infants and those with mature infants became progressively and rapidly greater as the weight of the premature infant fell below 5 lb., the difference being statistically significant.

TABLE 1

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN WOMEN WITH MATURE AND PREMATURE INFANTS IN THE SECOND WEEK OF THE PUERPERIUM

No. of Women	Birth Weight of Infants (lb. oz.)	Percentage		
		Entirely Breast Feeding	Partially Breast Feeding	Artificially Feeding
3,742	over 5 8	79·5	10·2	10·3
102	5 0 to 5 8	66·7	8·8	24·5
49	4 8 to 4 15	18·4	10·2	71·4
97	Under 4 8	6·2	2·1	91·8
248	Under 5 8	33·5	6·4	60·1

The duration of breast feeding after leaving hospital was studied in mothers with premature infants weighing 5 to 5½ lb. at birth. Women with premature infants weighing less than 5 lb. were not included because there were too few breast feeding their infants after leaving hospital for adequate data to be obtained. Forty-six women with premature infants were followed up after leaving hospital; of these, 37 were entirely breast feeding and nine were partially breast feeding when they were discharged. A similar follow-up was made on 471 women with mature infants, 302 of whom were entirely breast feeding and 169 partially breast feeding when they left hospital. The number and percentage of women in each group who breast

fed for one, two, three, four, five and six months was ascertained. The percentages for each series have been recorded in Fig. 1, and they show that

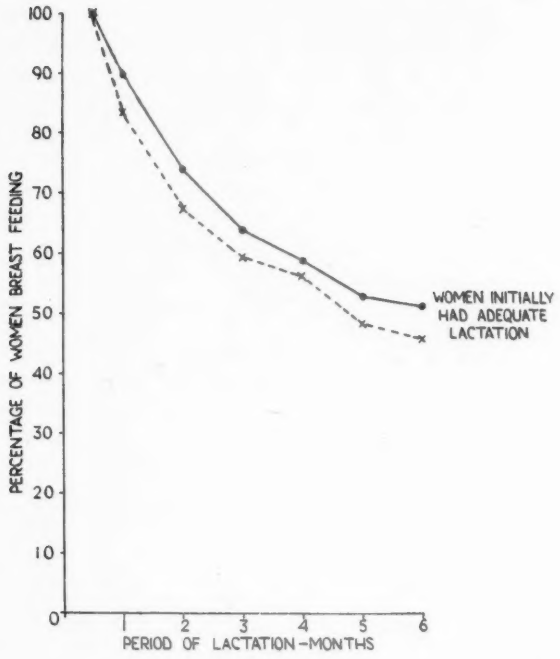

FIG. 1.

FIG. 1.—Duration of lactation in women with premature infants (×) compared with that of women with mature infants (●).

women with premature infants did not breast feed for as long as women with mature infants. The difference between the two groups was relatively small and it was not statistically significant. Thus women with premature infants weighing 5 to 5½ lb. were as successful in breast feeding between the third week and sixth month of lactation as those with mature infants. Nine women with infants weighing 5 to 5½ lb. at birth and with inadequate lactation on leaving hospital were followed up for six months. Only two of these lactated for the entire period. It is, however, impossible to draw any conclusion from results obtained from such a small series of cases.

Two-thirds of the women with premature infants failed to lactate adequately during the first two weeks of the puerperium, and according to the hospital records the incidence of premature babies leaving hospital was 6·2% of all live births. It therefore follows that in 4·1% of all mothers failure to lactate satisfactorily was associated with prematurity. This was an appreciable percentage and was probably largely due to the fact that the mothers of premature infants weighing under 5 lb. frequently went home during the second week of the puerperium leaving the infant in hospital and these infants were then bottle fed. Rarely was there any attempt to establish and maintain lactation by expressing the milk when the infants were unable to go to the breast because they were so frail and lacking in vitality. Thus women with premature infants were less successful in establishing lactation than women with mature infants, but once lactation was established in women with premature infants weighing 5 to 5½ lb. at birth, they appeared to progress as well as other women.

Abnormal Labour

Uterine Inertia. A study was made of the incidence and duration of breast feeding in 92 women who had primary uterine inertia during labour. The incidence of breast feeding, partial breast feeding and artificial feeding in the second week of lactation (usually on the tenth day of the puerperium) was determined. Similar observations were made on a control series of 6,464 women whose confinements were not complicated by uterine inertia. These were observed during the period of investigation. All these mothers had infants who were mature at birth. The results for the two series of observations are recorded in Table 2. They

TABLE 2

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN WOMEN WITH AND WITHOUT UTERINE INERTIA (CONTROL GROUP) IN THE SECOND WEEK OF THE PUERPERIUM

Group	No. of Cases	Percentage		
		Complete Breast Feeding	Partial Breast Feeding	Artificial Feeding
Uterine inertia ..	92	61	21	18
Control	6,464	78	8	14

show that the percentage of women with uterine inertia who were breast feeding in the second week of lactation is less than that of the control series of women. This difference (17%) is statistically significant.

Fifty-two women who had uterine inertia during labour were followed up after they left hospital to determine for how long they breast fed their infants; of these women, 37 were entirely breast feeding and 15 partially breast feeding their infants when they left hospital. The results were compared with those for a control series of 456 women, of whom 302 were entirely breast feeding and 154 were partially breast feeding when they left hospital. The number and percentage of women in each group who were

lactating at one, two, three, four, five and six months after the birth of their infant was determined and recorded graphically in Fig. 2, from which

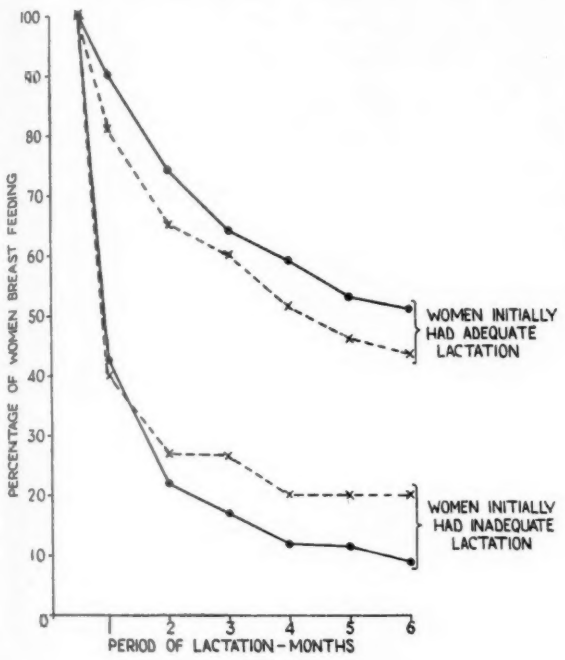

FIG. 2.

FIG. 2.—Duration of lactation in women with uterine inertia (×) compared with that of women without uterine inertia (●).

it is apparent that women who had uterine inertia and were entirely breast feeding their infants when they left hospital tended to lactate for a shorter time than did the control group, while women who had uterine inertia and were partially breast feeding when they left hospital tended to lactate for a longer time than the control group. This difference noted between the two groups of women who were initially entirely breast feeding their infants and that between the two groups who were partially breast feeding their infants was not statistically significant. Thus women with primary uterine inertia breast fed as successfully as other women between the third week and sixth month after childbirth.

The results of these investigations would suggest that primary uterine inertia or some associated abnormality impairs a woman's chances of initiating lactation successfully, but the effect is only slight and operates in the first two weeks of lactation. This type of uterine disorder is relatively rare, approximately 1% in women delivered in the Simpson Memorial Maternity Pavilion, and therefore can only be associated with an extremely small proportion of the many women who breast feed their infants unsuccessfully. Once lactation is established in women with uterine inertia, breast feeding continues as long as in other women.

Forceps Deliveries. Women who had been delivered of mature infants after the application of mid-cavity forceps were compared with a series of 2,952 who had had normal deliveries. The incidence of lactation in the second week of the puerperium and the duration of breast feeding beyond the second week were investigated in both series. The method of investigating the incidence and duration of breast feeding was the same as that for the previous investigation. The incidence of breast feeding, partial breast feeding and artificial feeding in both groups during the second week of lactation has been given in Table 3. It is apparent

TABLE 3

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN WOMEN WITH AND WITHOUT FORCEPS DELIVERIES (CONTROL GROUP) IN THE SECOND WEEK OF THE PUERPERIUM

Group	No. of Cases	Percentage		
		Complete Breast Feeding	Partial Breast Feeding	Artificial Feeding
Forceps	160	61	23	16
Control	2,952	81	12	7

from this table that the number of women with forceps deliveries who were entirely breast feeding their infants in the second week of the puerperium was less than among the control group of women, the difference between the two groups being 20% which is statistically significant.

Observations were made on a series of 65 women who had forceps deliveries to discover the duration of their lactation. Forty-nine were entirely breast feeding and 16 partially breast feeding their infants in the second week of the puerperium. The results of these observations were compared with those obtained for a control series of 492 women, of whom 292 were entirely breast feeding and 190 were partially breast feeding in the second week of the puerperium. The percentage of women in each group who breast fed for one, two, three, four, five and six months was calculated and is recorded in Fig. 3, from which it is apparent that women who leave hospital after forceps deliveries breast feed their infants as long as other women. This applies to women who were initially entirely breast feeding. No conclusion could be drawn from the results for those who were partially breast feeding in hospital because there were too few.

It would appear, therefore, that women who have undergone mid-cavity forceps deliveries are slightly less likely to breast feed their infants satisfactorily during the first two weeks of lactation, than are women who are delivered normally, but that once lactation is established they are able to feed their infants for as long as other women. The difficulty in lactation following this type of delivery, however, can play only a minor role in reducing the incidence of lactation among women in general since only 6% (approximately) of women leaving hospital with their infants had undergone high forceps deliveries.

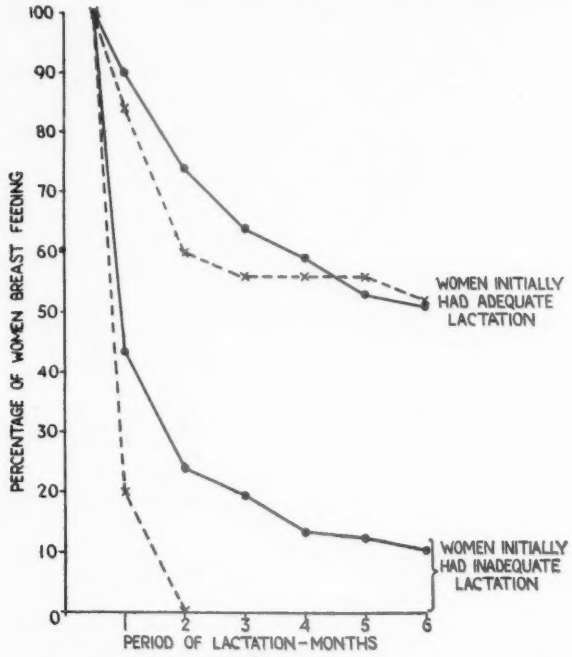
PERCENTAGE OF WOMEN BREAST FEEDING
PERIOD OF LACTATION-MONTHS
WOMEN INITIALLY HAD ADEQUATE LACTATION
WOMEN INITIALLY HAD INADEQUATE LACTATION

FIG. 3.

FIG. 3.—Duration of lactation in women with forceps deliveries (×) compared with that of women without forceps deliveries (●).

Caesarean Section. A series of 162 women delivered by Caesarean section and a control series of 2,952 delivered normally were investigated to determine their ability to breast feed their infants both with regard to the establishment of lactation and its duration. All these women had mature infants. In both series the incidence of breast feeding, partial breast feeding and artificial feeding on the tenth to fourteenth day of the puerperium was ascertained and the results recorded in Table 4. These results showed that only 59% of those women who had had a Caesarean section were entirely breast feeding their infants on the fourteenth day after labour. This was 22% less than that in the control group of women, a statistically significant difference.

The duration of lactation was determined in a series of 69 women delivered by Caesarean section and in a control series of 486 women who were delivered normally. In the second week of the puerperium 49 of the 69 women in the first series were entirely breast feeding, and 20 were partially breast feeding, whereas in the control series 292 women were wholely breast feeding and 184 were partially breast feeding their infants. The women entirely breast feeding and those partially breast feeding were investigated separately, and the number and percentage of women in each of these groups who breast fed for one, two, three, four, five and six months was noted. The percentages are recorded in Fig. 4 and show that 70% of women

TABLE 4

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN WOMEN WITH AND WITHOUT CAESAREAN SECTION (CONTROL GROUP) IN THE SECOND WEEK OF THE PUERPERIUM

Group	No. of Cases	Percentage		
		Complete Breast Feeding	Partial Breast Feeding	Artificial Feeding
Caesarean ..	162	59	19	22
Control	2,952	81	12	7

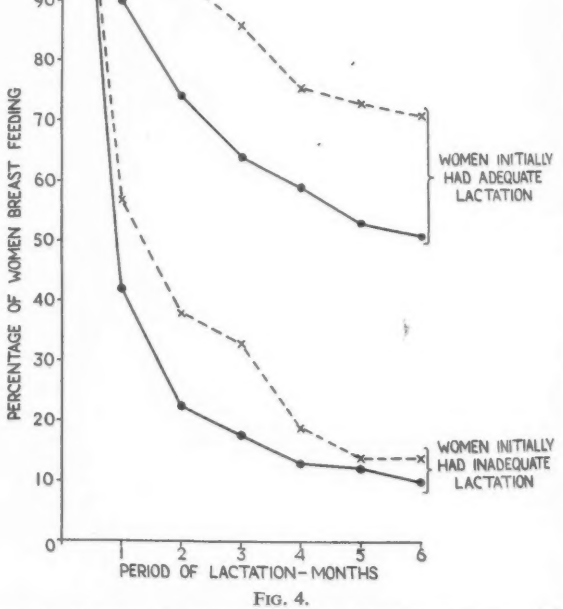
PERCENTAGE OF WOMEN BREAST FEEDING
PERIOD OF LACTATION-MONTHS
WOMEN INITIALLY HAD ADEQUATE LACTATION
WOMEN INITIALLY HAD INADEQUATE LACTATION

FIG. 4.

FIG. 4.—Duration of lactation in women with Caesarean section (×) compared with that of women without Caesarean section (●).

who had a Caesarean section and were initially entirely breast feeding their infants continued to do so for at least six months. This is 20% more than the comparable group, a difference which is statistically significant. Women belonging to both series, however, who were partially breast feeding in the second week of their puerperium usually weaned their infants prematurely. The tendency did not differ appreciably in the two series.

It would appear, therefore, from these investigations that Caesarean section reduces the incidence of adequate lactation during the first two weeks of the patient's puerperium. This may be due to the mother's impaired state of health or delay in starting breast feeding or to a combination of these factors. Since 6% (approximately) of women leaving hospital with their infants are delivered by Caesarean section, this reduction has only a small but appreciable effect upon the incidence of breast feeding amongst women delivered in hospital as a whole. Those mothers, however, who have undergone Caesarean section and are able entirely to breast feed their infants by the fourteenth day are more likely to continue for six months than normally delivered mothers. This may be due to their increased length of stay in hospital, 71% remaining two weeks and 27% at least three weeks, while almost all women with normal deliveries are discharged on the tenth day. The incidence of premature weaning among mothers who are not fully breast feeding by the fourteenth day after operation is high, but does not differ appreciably from that of normally delivered mothers who fail to lactate adequately by the second week of the puerperium. Thus Caesarean section has a deleterious effect upon the establishment of lactation, but no adverse effect upon its duration once it is adequately established.

Summary

Investigations have been made on women who were delivered of live born infants in hospital to determine both the incidence of breast feeding, partial breast feeding and artificial feeding in the second week of the puerperium and the duration of breast feeding.

The results of the investigation on the type of infant feeding in the second week of the puerperium showed that women with premature infants, and those who had uterine inertia, mid-cavity forceps deliveries or Caesarean section were less successful in entirely breast feeding their infants than other women. It was estimated that in 4% of all mothers failure to lactate satisfactorily was associated with prematurity, while in considerably less than 1% of all mothers failure to lactate satisfactorily was associated with uterine inertia, forceps deliveries or Caesarean section. Possible causes of the apparent impairment in lactation have been given.

The conclusion drawn from the follow-up of women from the third week to sixth month after their infants were born was that the percentage of women who prematurely weaned their infants during that period was not influenced by the mother having premature infants, uterine inertia, forceps deliveries or Caesarean section.

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PART III. ABNORMALITIES OF THE BREAST

In lactating women psychological disorders and pathological conditions, particularly those associated with marked pyrexia (König. 1939; Herlitz, 1946; Ström, 1947) are liable to limit success in breast feeding. Ill health, however, plays only a minor part in this respect in comparison with abnormalities of the breast, and in the light of our present knowledge it appears that acquired abnormalities of the mammary gland and nipples are more often associated with impaired lactation than those of congenital origin (Spence, 1938; Engel, 1947; Robinson, 1942).

Review of the Literature

The recorded incidence of fissured nipples in women delivered in hospital during the first two weeks of lactation varies between 6 and 50% (Robinson, 1942; Gunther, 1945), and it has been stated that women so affected are more prone to have difficulty in breast feeding their infants than are those with normal nipples (De Lee and Greenhill, 1947; Robinson, 1942). These authors, however, do not give the details on which their statements are based nor do they assess the frequency of premature weaning among women with fissured nipples.

Both Norval (1947) and Waller (1938, 1943) have studied the effect of breast engorgement upon lactation and have stated that women with all grades of this condition may fail to breast feed their infants successfully, but that those with severe breast engorgement frequently wean their infants earlier than do those with milder degrees of engorgement. Norval (1947) showed that only women with the severest degree of engorgement, that characterized by enlargement and excessive hardness of the breast lasting for more than four days (2·4% of his series), found more difficulty in breast feeding than other women, while Waller (1938) gave the impression that all grades of engorgement were responsible for women weaning their infants prematurely. Some women, however, experience no engorgement of the breast and in some the breast enlargement is delayed, absent or hardly detectable. Such women may also have difficulty in breast feeding their infants. In Norval's (1947) series of 462 women 13·8% fell into this category, and of these half had inadequate lactation. According to Waller (1938) this type of woman usually experiences no difficulty in breast feeding. There is, therefore, lack of agreement upon the relationship between breast engorgement and breast feeding.

In the past mastitis has accounted for a high proportion of cases of premature weaning. The infants were weaned within a few days of the onset of the disease because it was considered best for both the mother, who was able to rest the affected breast, and the infant, who was protected from the risk of gastro-enteritis due to taking the infected milk (Moon and Gilbert, 1935). The same authors noted that in 33% of cases the mother had no option but to wean her infant because she developed bilateral mastitis. Moreover, breast feeding was not very practical in those women who required operation (24 to 75%). König (1939), who studied 102 women with mastitis, found that only 34% of them were able to breast feed their infants entirely on the tenth day of lactation as compared with 66% of a control series of women. Robinson (1942) confirmed König's conclusion but did not give details of her investigation. About 9% of all lactating women have acute mastitis and approximately 10% of these women develop the disease in the first two weeks of lactation (Fulton, 1945). There is no doubt that lactation is markedly affected by mastitis, but whether it is so frequently terminated because of the disease now that antibiotic therapy has been introduced, is a matter for consideration.

Method

Separate investigations were made into the relationship of each of the abnormalities, fissured nipples, breast engorgement and mastitis, to (*a*) adequacy of lactation in the second week of the puerperium and (*b*) duration of lactation beyond the second week of the puerperium. The same methods of investigation were used throughout. Adequacy of lactation was assessed by first studying the incidence of breast feeding, partial breast feeding and artificial feeding on the fourteenth day of the puerperium or earlier if the woman was discharged from hospital before that time. The duration of lactation beyond the second week of the puerperium amongst women who were completely breast feeding or partially breast feeding their infants in the second week was determined by noting the number of such women who breast fed for one, two, three, four, five and six months. In each investigation the results were compared with those for a control series of women who had none

of the abnormalities under discussion. Women with premature infants were not included in any of the investigations or control series.

Fissured Nipples

Two hundred and eighty-eight women who developed fissured nipples while in hospital were investigated. In each case a record was made of the day of the puerperium on which the fissured nipples were first detected. The results were divided into two groups, one for women who developed fissured nipples before the sixth day of the puerperium and another for those who first had fissured nipples either on or after the sixth day of the puerperium. Each of these groups was subdivided to show those mothers who were entirely breast feeding, partially breast feeding or artificially feeding their infants at the end of the second week of the puerperium; the number in each subgroup is noted in Table 1. A control series of 3,454 women who were free from any abnormality of the nipple during the first two weeks of the puerperium was investigated and subdivided in the same way. The results are also recorded in Table 1. A comparison of the two sets of results shows that the number of women with fissured nipples who were breast feeding completely was lower than that for the control group of women. This difference in incidence (31%) was statistically significant. It was also apparent that this difference was greater when women who developed fissured nipples on or after the sixth day of the puerperium were compared with the control series (41%) than when women with fissured nipples before the sixth day of the puerperium were compared with the control series (22%).

Women who had fissured nipples during the first two weeks of lactation were followed up to decide whether they breast fed their infants for as long as a control series. Of the 185 women with fissured nipples investigated, 124 were entirely breast feeding and 61 were partially breast feeding in the second week of their puerperium. The duration of lactation in each case was determined. The results were subdivided to show the duration of lactation among women in whom fissured nipples were noted before the sixth day of the puerperium and among those in whom fissured nipples were first noted on or after the sixth day of the puerperium. Similar observations were made on a control series of 388 women who had not suffered from fissured nipples; of these 280 were initially entirely breast feeding and 108 were initially partially breast feeding on the day of discharge from hospital. The results of the follow-up of both these series are recorded in Table 2. They show that the control series of women tended to breast feed for longer than the series of women with fissured nipples. A statistical analysis was made of the differences between the results of the control series and of mothers with fissured nipples before the sixth day of the puerperium, and between the control series and mothers with fissured nipples on or after the sixth day. Only the difference between the control series and that of women with fissured nipples on or after the sixth day who were entirely breast feeding in the second week of lactation was statistically significant.

TABLE 1

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN WOMEN (A) WITH FISSURED NIPPLES ON OR BEFORE THE FIFTH DAY OF THE PUERPERIUM, (B) WITH FISSURED NIPPLES AFTER THE FIFTH DAY, (C) WITH NORMAL NIPPLES

Group	No.	Percentage		
		Completely Breast Feeding	Partially Breast Feeding	Artificially Feeding
A	144	60	31	9
B	144	41	41	18
C	3,454	82	8	10

TABLE 2

DURATION OF LACTATION IN WOMEN (A) WITH FISSURED NIPPLES ON OR BEFORE THE FIFTH DAY OF PUERPERIUM, (B) WITH FISSURED NIPPLES AFTER THE FIFTH DAY, (C) WITH APPARENTLY NORMAL NIPPLES

Group	No.	Initial Lactation	Percentage Lactating Each Month						
			½	1	2	3	4	5	6
A	58	Adequate	100	74	60	55	46	46	45
B	66	Adequate	100	67	39	32	27	24	21
C	280	Adequate	100	90	74	64	59	53	51
A	20	Inadequate	100	30	20	15	10	10	10
B	41	Inadequate	100	49	19	15	15	15	12
C	108	Inadequate	100	41	24	19	13	12	9

It would appear that women with fissured nipples were less successful in establishing and maintaining lactation than those without such an abnormality, the degree of impairment being statistically significant in women whose nipples became fissured after the fifth day of lactation and not in those who developed fissures before that stage. The cause of this difference is obscure. It is possible that the aetiology of the fissures in the first group differs from that of the second. For instance, the disorder occurring in the first few days after parturition may be predominantly due either to faulty management of the initial stage of breast feeding or to the infant failing to fix properly on the breast, while that occurring after the first week may be predominantly due to a failure to establish an adequate milk flow.

Breast Engorgement

The incidence of breast feeding in a group of 147 women with severely engorged breasts was compared with that in a control group of 3,595 women. The diagnosis of severe engorgement depended on either the presence of undue firmness of the mammary gland or of oedema of the breast associated with much local tenderness and pain and possibly a subnormal flow of milk. In all cases treatment was considered necessary and consisted of either emptying the breast or leaving the milk in the breast. In a few cases the breast was bathed with hot or cold water. Stilboestrol therapy was not used. The number of women in each group who were entirely breast feeding, partially breast feeding or artificially feeding their infants in the second week of lactation, was determined and the results are noted in Table 3. These show that

TABLE 3

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN WOMEN (A) WITH AND (B) WITHOUT EXCESSIVE BREAST ENGORGEMENT

Group	No.	Percentage		
		Completely Breast Feeding	Partially Breast Feeding	Artificially Feeding
A	147	60	31	9
B	3,595	80	10	10

the incidence of breast feeding in the group of women with engorged breasts was less than in the control group. This difference (20%) is statistically significant.

The duration of breast feeding in mothers with severe engorgement of the breast was also investigated and the results compared with those for a control group of women who had not suffered from severe engorgement. For this investigation 78 women who had had engorged breasts during the puerperium were followed up for six months. Of these, 48 were entirely breast feeding and 30 were giving their infants complementary feeds when they left hospital. Of the control group of 471 women, 296 were entirely breast feeding and 175 were partially breast feeding their infants in the second week of the puerperium. The results of both the series under investigation and of the control series are given in Fig. 1. They show that

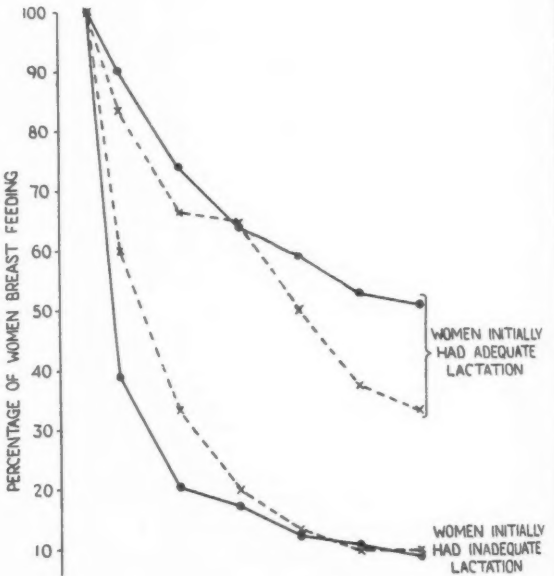

FIG. 1.—Duration of lactation in women with breast engorgement (×) compared with that of women without breast engorgement (●).

33% of women who had engorged breasts and were initially breast feeding continued to breast feed their infants for six months, while 51% of the comparable control group breast fed for the same period of time. This difference between the two groups (18%) is statistically significant. A similar comparison between the same groups of women who were initially partially breast feeding showed that the duration of lactation in the two groups did not differ appreciably.

The results of this investigation into breast engorgement showed that neither the incidence nor duration of breast feeding in women with severe engorgement of the breast was as satisfactory as

in other women delivered in hospital. However, compared with the number of women in hospital, the number treated for engorgement of the breast was small and did not exceed 5%. Thus, the percentage of all cases of inadequate lactation resulting from engorged breasts is only a fraction of 5%.

Mastitis

The incidence and duration of lactation in women who developed mastitis have been investigated. The incidence of complete breast feeding, partial breast feeding and artificial feeding in the second week of the puerperium was determined in a series of 92 women who had developed mastitis and in a control series of 2,919 women who had no mammary infection. The results are recorded in Table 4. They show that 80% of mothers in

TABLE 4

INCIDENCE OF DIFFERENT TYPES OF INFANT FEEDING IN WOMEN (A) WITH AND (B) WITHOUT MASTITIS

Group	No.	Percentage		
		Completely Breast Feeding	Partially Breast Feeding	Artificially Feeding
A	92	61	21	18
B	2,919	80	10	10

the control series and 61% in the series with mastitis entirely breast fed their infants in the second week of the puerperium. This difference (19%) is statistically significant.

The duration of lactation beyond the second week of the puerperium in 42 women who developed mastitis during the lying-in period was investigated, and at the same time similar observations were made on a series of 495 women who had not suffered from mastitis. Of the women with mastitis 32 were entirely breast feeding and 10 were partially breast feeding in the second week of the puerperium, but of the control series 300 were entirely breast feeding and 195 partially breast feeding in the second week of the puerperium. The results of the investigation are given in Fig. 2. The comparison between the two groups shows that slightly more women in the mastitis group and initially entirely breast feeding were successful in breast feeding for six months than in the comparable control group, but this difference (4%) is not statistically significant. A similar comparison between the two groups of women who were initially partially breast feeding was made; 20% of those who had mastitis and 9·2% of those belonging to the control group breast fed their infants for six months. No conclusion, however, could be drawn from the results of such a small series of observations.

This investigation has shown that mastitis lowers the incidence of breast feeding in the second

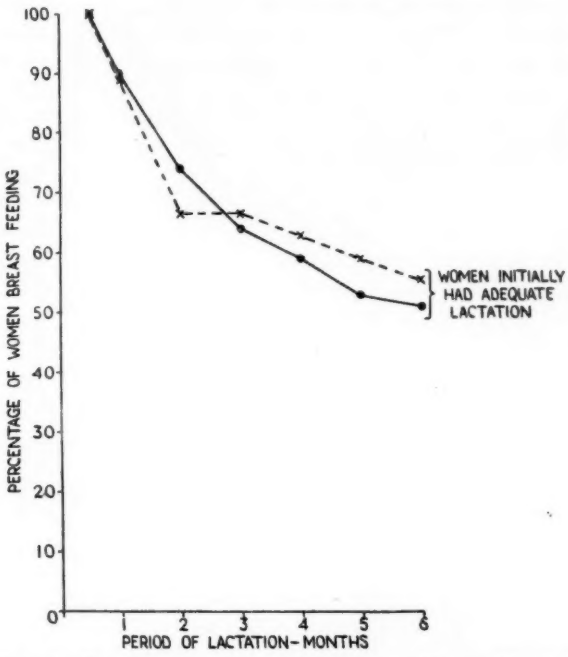

FIG. 2.—Duration of lactation in women with mastitis (×) compared with that of women without mastitis (●).

week of the puerperium. Thereafter, the course of lactation in women who were breast feeding during the second week did not differ apparently from that of other women. The hospital statistics showed that approximately 1% of all lying-in women developed mastitis in the first two weeks of the puerperium. It is apparent, therefore, that mastitis accounts for an extremely small proportion of women having inadequate lactation. It appears from a comparison of these observations with those made by both Moon and Gilbert (1935) and König (1939) that mastitis did not impair the course of lactation in the present series as markedly as it has done in past series. This is probably due to the relatively recent introduction of antibiotic therapy and a reduction in the surgical treatment of mastitis.

Summary

The influence of fissured nipples, excessive breast engorgement and mastitis upon the course of lactation in women who had their confinements in

hospital has been investigated. The incidence of breast feeding, partial breast feeding and artificial feeding in the second week of the puerperium and the duration of lactation was determined. The results of these observations showed that women with fissured nipples were less successful in establishing lactation than other women. The women who developed fissured nipples after the fifth day of lactation more frequently had difficulty in breast feeding than those who had fissured nipples before that time. After leaving hospital the course of lactation in women who developed fissured nipples after the fifth day of the puerperium was less satisfactory than that of normal women or even of women who developed fissured nipples in the earliest days of lactation.

Women with excessive breast engorgement had greater difficulty in establishing and maintaining lactation than a control group of women.

Mastitis reduced a woman's chances of entirely breast feeding her infant in the second week of her puerperium. The course of lactation after that period was as satisfactory as that in women who had no history of mastitis. The greater success in breast feeding amongst the present series of women with mastitis compared with that for older series was attributed to the introduction of antibiotics in treatment of the disease.

Fissured nipples, breast engorgement or mastitis accounted for a very small proportion of women failing to breast feed their infants satisfactorily.

I wish to thank the Paediatric Staff of the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh, for permission to study their case records. I am indebted to Dr. D. N. Lawley for his assistance in the statistical analysis.

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BOOK REVIEWS

Maternal Care and Mental Health. By JOHN BOWLBY. 1951. Geneva: World Health Organization Monograph Series. London: H.M. Stationery Office. Pp. 179. Price 10*s*.

This brilliant and painstaking study leaves no doubt in the mind as to the importance of individual maternal care in the mental and physical well-being of all children. An uneasy conviction, rightly fostered by Bowlby and others in this country, has been growing that much official time and public funds are spent in doing the worst possible for the young child when he is removed from a bad home, and placed in a good Home. In this monograph, the author states his views clearly and vigorously, and supports them ably by his energetic survey of material from Europe and U.S.A. The bibliography covers the whole field of child care in the last 20 years or so, when in the period between two world wars and the economic depressions and social upheavals of the intervening years, this problem has become so clearly delineated in the minds of all who care for the child who is temporarily or permanently deprived of a normal upbringing in his own family home. The enquiry specifically excludes child refugees from war or other causes; even without this pathetic addition the problem is of formidable dimensions, and the author deserves and will doubtless receive unstinted praise for his grasp which has enabled him to reduce such a mass of material to the compass of this readable monograph.

His thesis, succinctly stated on p. 47, is that deprivation, for any cause, of a mother-figure in the early years of childhood may so imperil necessary stages in emotional development that the child may develop permanently an affectionless psychopathic character owing allegiance to no one, or may regress to such a point of emotional, mental and physical apathy that he remains permanently under-developed. The effects of lack of early care may be reduced (Goldfarb) if individual mothering is instituted before 12 months, but he regards the damage as likely to be permanent if delayed beyond 2½ years. The limits of vulnerability are uncertain and much further research is needed to clarify this point, and also to seek an explanation for the apparent immunity of some children to these effects. As Bowlby rightly points out, some children are apparently immune to the effects of tubercle-infected milk, but that does not make it right for them to risk drinking it.

The direct evidence is briefly reviewed, and there is alarming uniformity in many of the follow-up reports cited. Alongside these are welcome indications, for instance in the Curtis report, of an awareness of this great problem. However, the official mind moves slowly away from the convenience of the beaten track, and even the paediatricians have not been guiltless in this matter of putting physical care first at the expense of the possibility of a normal emotional development. Both direct studies of deprivation and follow-up studies of the behaviour of deprived children tally with the evidence, much of it from psychoanalytic studies, that the crucial point lies in the infant's and young child's inability to pursue his development independently of some individual supporting figure to whom he may consistently turn for help, encouragement and refuge. Out of this relationship he develops in himself integrity and independence. Further research is called for, and suggestions are made as to the lines such research might follow. (The author is himself actively engaged upon one such group research.)

The problems of prevention are perhaps less simple than they would seem to be, even if Bowlby's thesis is wholly accepted. In his chapter on the illegitimate child he brings evidence to show that in a high proportion of cases the unmarried mother has a very poor chance of maintaining her child, a chance which tends to lessen as the years go on. Even where the child is accepted and brought up by maternal grandparents there is often a great deal of normal emotional security lacking in his nurture. The remedy of adoption at an early age is unequivocally advocated, and the view is put forward that most unmarried mothers can be helped to accept this as a necessary step in a realistic frame of mind, taking the long view. The author also claims, rather surprisingly, that intelligence tests in the early months are of no predictive value whatever, a view which brushes aside Gesell's claims. But his statement is well supported by the evidence he quotes, and certainly the predictive value of an early intelligence test on a disturbed baby who had not settled to a normal home routine, and given by relatively inexperienced workers, is probably of very little use. Thus early adoption is certainly important from all sides. But it must be recognized that adoption has its own problems, and that the vast social and emotional problem which lies behind the undoubted fact of large numbers of parents willing to adopt illegitimate babies, is something which must be reckoned with. Here again is a suggested line of research, that of careful follow-up of illegitimate children whose mothers have been helped to accept full responsibility for their care. What is to be avoided at all costs is a mechanistic solution to what is essentially an individual human problem.

This monograph does in fact go far to show how true it is that very few deprived children come from normal families as a result of sheer misfortune, and that a very high rate of personality factors is present in the parents of such children. That the need is for more work,

undertaken from the psychiatric angle, no one could doubt after reading this challenging report.

Speech Habilitation in Cerebral Palsy. By MARION T. CASS. 1951. Columbia University Press; Oxford University Press (London: Geoffrey Cumberlege). Pp. 198. Price 20*s*. ($3.00).

This book is a study of the aetiological, therapeutic and educational aspects of cerebral palsy with special reference to speech habilitation. The author begins with a comprehensive description of causative factors and effects, and follows with a résumé of the therapeutic principles and practices of muscular re-educational therapy for cerebral palsy as applied by Dr. Winthrop Morgan Phelps.

Dr. Cass's technique of speech treatment is based primarily on relaxation and the teaching of correct breathing and sound articulation. She outlines a detailed programme of work. Although the varying types of cerebral palsy are mentioned there is no reference to the handling of the concomitant speech disturbances; a single method is carefully explained without any variation to cover the wider aspects of the problem of speech and language disorders in cerebral palsy.

The title of this book is misleading; its value lies not specifically in speech habilitation, but in its insight and understanding of the cerebral palsy problem as a whole. The author writes with experience. She strikes at the heart of the problem when she indicates the importance of psychological understanding, guidance and encouragement in the handling of the individual; the necessity for treating 'the whole child'; the inadequacy of testing intellectual ability in cerebral palsy by formalized and standardized tests; and finally the urgency for extending the facilities for cerebral palsied children by means of educational and therapeutic centres staffed only with people suitably equipped in personality, intelligence and temperament to meet the many demands in this specialized field.

Differentialdiagnostische Symptomatologie von Krankheiten des Kindesalters. By W. CATEL. 1951. Stuttgart: Georg Thieme. Illustrated. Pp. 640. 2nd edit. Price DM. 69.

As the first edition of this pleasant book was published in Germany in 1944 it has probably not achieved as wide a recognition as it deserves. This second edition is beautifully produced and contains many illustrations of a high order.

As the title implies, the subject matter is concerned with symptomatology and deductions to be drawn from the various manifestations of disease in children. Thus, the book does not set out to be a textbook of children's diseases, some children's complaints are not even mentioned, and treatment is not considered.

Little distinction is drawn between symptoms and signs, and the two are discussed in suitable groups almost in the form of lectures. The author clearly brings a wealth of clinical experience to his subject, which is presented concisely and without unduly long sentences.

A criticism of the book is that some of the sections seem to be insufficiently up to date, which may be accounted for by the fact that the author has consulted only continental publications for his recent advances. But such criticism does not seriously detract from the main purpose of the book, the consideration of symptomatology, and all physicians, and particularly those engaged in the teaching of paediatrics might find its orderly presentation stimulating and helpful.

Die Hämolytischen Syndrome im Kindersalter. By C. GASSER. 1951. Stuttgart: Georg Thieme. 101 text figures. Pp. 308. Price DM. 45.

This monograph on the haemolytic diseases of children comes from the Children's Hospital, Zurich, and both its background and its subject matter will ensure for it a warm welcome. The development of new techniques has given an impetus to the investigation of the mechanisms of blood destruction, and Dr. Gasser has obviously at his disposal a vast amount of clinical material for analysis. Throughout his book the application of these techniques to problems both old and new is discussed and illustrated by a wealth of case reports.

Photomicrographs and line drawings of unusual clarity enhance the value of the book, and the production is of the high standard we have come to associate with the publishers.

Zahnarztliche Probleme in der Kinderheilkunde. By F. PERABO. 1951. Basel: Benno Schwabe & Co. 121 text figures. Pp. 120. Price Sw. Fr. 14.50.

This is an excellent little guide for the paediatrician and general practitioner in matters relating to diseases of the teeth and mouth. It covers a wide field without too much detail, rightly placing most emphasis on diagnosis. The illustrations are plentiful and clear. There is no doubt that it will be found very useful especially as regards disorders of the teeth. It is more doubtful whether sufficient detail is given to enable lesions of the mucosa to be so well distinguished. The teaching differs in some parts from that usually used here, and most of the references are to standard works in the German language to which the practitioners presumably have access. Summaries of several Swiss investigations which are not compared with results elsewhere are doubtless chosen as most likely to interest Swiss readers.

Second Annual Report of the International Tuberculosis Campaign, July 1949-June 1950. The International Tuberculosis Campaign, Copenhagen. London: Wm. Heinemann Medical Books Ltd., 1951. Pp. 334. Price 7*s*. 6*d*.

The 'I.T.C.' was a joint enterprise undertaken by U.N.I.C.E.F. and the Scandinavian voluntary organizations for a B.C.G. mass campaign. This is their report of the years 1949-1950.

It includes sections on finance, on the laboratories, on publicity and on the compilation of statistics.

The best chapter is that entitled 'Field Operations' in Part III, which describes the actual organization and technique used in the field. It was found best to divide each country up into areas, and then to concentrate on

one area at a time and finish the campaign in that area, before moving on to the next. Publicity was otherwise too much in advance of the actual work and enthusiasm waned before vaccinations were done.

The latter part of the report deals with the campaign in different countries, and the whole volume is a reference book rather than a text book.

The Conference on European B.C.G. Programmes, September, 1949. The International Tuberculosis Campaign, Copenhagen. London: Wm. Heinemann Medical Books Ltd. 1951. Pp. 333. Price 7*s.* 6*d.*

This is a report of the Conference held in Copenhagen in 1949 to review critically experience gained from mass vaccination campaigns in various countries.

It is full of useful information for anyone engaged on B.C.G. vaccination. Particularly valuable are the three sections by Ustvedt on the technique of tuberculin testing, local reactions to B.C.G., and tuberculous disease in vaccinated persons.

Growth and Development of Children. By E. H. WATSON and G. H. LOWREY. 1951. Chicago: The Year Book Publishers, Inc. 54 text figures. Pp. 260. Price $5.75.

The book presents an outline of the growth and development of the normal child. The chapters include discussions on heredity, prenatal and postnatal environment, foetal growth and behaviour, foetal nutrition, normal physical measurements, including the use of the Wetzel grid, Fels composite sheet and other methods of assessing physical status, the development of organs, such as the heart, bone development, energy metabolism, nutrition and behavioural development. The authors have only attempted an outline of the subjects discussed, but supply useful references for further reading. There are many tables which will be of value to all concerned with child care.

The book is for the most part factually accurate and up to date. It pays much more attention to physical than to behavioural development. The development of behaviour is very sketchily covered, with a table of milestones for 4, 16, 28, 40 and 52 weeks; 15, 18, 24, 36, 48 and 60 months, with an insufficient definition of what is meant by the milestones mentioned. The book is essentially a presentation of facts, but there is not enough about their clinical application, about the normal variations which occur (except in the section on weight and height), and about the various factors which always have to be considered in the assessment of an individual child. The book would not help one much to decide whether an individual child is normal or not, but it does give a useful summary of facts which all concerned with children should know about their growth and development.

The 1951 Year Book of Pediatrics (July 1950-June 1951). Edited by H. G. PONCHER in collaboration with J. B. RICHMOND and I. A. ABT. 1951. Chicago: The Year Book Publishers Inc. Illustrated. Pp. 441. Price $5.00 or 40*s.*

This annual is as convenient in size and as attractively produced as ever, and is an admirable guide to current paediatric thought and practice.

The subject matter consists of clear and objective summaries of those papers published during the previous 12 months which the editors thought worthy of abstracting. It is obvious that their problem has been not so much what to include as what to leave out, and the individual reader must judge for himself how successful they have been. The abstracted papers are grouped together into suitable chapters, to each of which there are a few introductory editorial paragraphs designed to summarize or reorientate the year's publications. As in previous years, there is a sprinkling of editorial comments throughout, which the reviewer sometimes found irritating and often better omitted.

It is unfortunate, now that paediatric publications in Europe and elsewhere are getting back to their pre-war state, that more space is not given to them. Only about one-sixth of the volume deals with papers published outside the United States, and it is fair to suggest that in future the title might be changed to the 'Year Book of American Pediatrics'.

Diseases of Infancy and Childhood. By WILFRID SHELDON. 1951. London: J. & A. Churchill Ltd. 6th edit. Illustrated. Pp. 812. Price 40*s.*

We welcome the sixth edition of this well known book. Like most of us, it has grown somewhat stouter with the years, but it is still portable, readable and reliable. The first edition was published in 1936, and was thus written in a different therapeutic era. The development of antibacterial substances for systemic administration has been associated with changes in the incidence, symptoms, signs, treatment, and prognosis of disease, and the author has re-written and re-edited his own work with these changes in mind. There have been other developments in paediatrics in the same period, and descriptions of several are included for the first time. Four vivid colour plates also enhance the attractions of this new edition.

Pediatric Allergy. By R. CHOBOT. 1951. London: McGraw Hill Publishing Company. 1st edit. Pp. 284. Price 38*s.* 6*d.*

It is difficult not to be influenced by the prejudice aroused against a book by consistently bad grammar and a phraseology so loose that the meaning is often uncertain. Many American authors use words and expressions differently from English writers, often to advantage, and just occasionally the author of this book uses a phrase which is pithy and direct. Unfortunately most of the book is written in a style which suggests that it has been dictated in a hurry and never corrected, with references to other papers inserted with little regard for their critical value. An occasional misprint is to be expected, and there is a curious error on the first page of this book which would seem to be a misprint but which, such is the author's use of words, may even be intentional.

The book is well set out in that the various problems of allergy in childhood are given reasonable space and the theory, pathology, diagnostic procedures, treatment and particular diseases receive adequate consideration. The chapter on diagnostic procedures is fairly clear and useful, but the removal of 25 ml. of blood from children under the age of 3 years does not recommend itself as

a method of choice in diagnosis. There is much elsewhere that would be of interest if the writing were more critical and if such surprising statements were not made so blandly and so often. The description of the pathology involves inflammation as an essential part of allergy, and such conditions as eosinophil granuloma and migraine are unquestioningly accepted as entirely allergic. The removal of septic foci by tonsillectomy and so on is strongly recommended for the cure of all sorts of allergic conditions, and an appendix of case histories, all with happy endings, helps to underline the value of this.

The loose writing and confused thinking manifested throughout so much of the book make it difficult to know when the author's opinion is of value, and consequently it is difficult to recommend the book for general reference or reading.

La Talassemia. By G. ASTALDI, P. TOLENTINO and C. SACCHETTI. 1951. Pavia: Biblioteca Haematologica. 69 text figures. Pp. 229. With English summary. Price Lira 2,500.

The monograph is divided into two sections. The first devotes chapters to the genetics of thalassaemia, the symptomatology and radiological findings, the peripheral blood picture, the bone marrow, morbid anatomy, the clinical and pathological forms of the disease in detail, and diagnosis, prognosis and treatment. The second section reports the researches of the authors, and details their experiments. Each chapter is profusely and well illustrated by photomicrographs and line graphs.

Throughout their treatise the authors divide the disease into three definite forms: *major*, occurring in the offspring of two affected parents, and synonymous with Cooley's anaemia: *minor* (or Rietti's disease) where the affected person is heterozygous yet shows the disease clinically; and *minima*, where the heterozygous individual has no clinical manifestation though the haematological picture is that of the minor form in a lesser degree. Stress is laid on the diagnostic facies seen in the major form. Their experimental work points to some factor closely connected with the biology of the erythron as the abnormality, this factor being intrinsic and producing increased red cell fragmentation. Lysis and phagocytosis are of minor importance, the plasma shows no abnormality, and the splenomegaly is entirely mechanical, resultant upon cell debris storage.

The references are numerous and cover the world literature, while the only criticism to be offered is that the reader is often lost in the wealth of detail offered.

Psychiatrie Sociale de l'Enfant. Edited by C. HOERSPERNIK. 1951. Paris: Le Centre International de l'Enfance. 11 text figures. Pp. 535. Price Fr. Fr. 2,500.

This is a nearly complete collection of the lectures given at a course in the social psychiatry of the child organized by the International Children's Centre and held in Paris and London from October 15 to December 15, 1950. Some 54 lecturers contribute 64 lectures, which should be read in the original by those interested in the subject.

Great Ormond Street Journal

The *Archives* is at the moment the only paediatric periodical in Great Britain, and with the increasing interest in paediatrics in general there must therefore surely be much work of great interest which at present does not get published. At Great Ormond Street, for example, the home of English paediatrics, a wide range of clinical and pathological investigations is constantly being undertaken and the results, both success and failures, should be made available to other workers.

It is fitting that the first extra journal to be published should come from Great Ormond Street. The Board of Management is to be congratulated on this courageous venture; all will wish it well.

The Journal is published by H. K. Lewis and Co., and costs 7*s* 6*d*. The appearance of future issues will be at approximately six-monthly intervals, but obviously in any 'Proceedings' such as these, the exact interval must vary.

In commending the journal to readers of the *Archives*, we wish it long life and success. It will be a worthy addition to lie beside the *Archives* in departmental libraries and will prove of value and interest to all paediatricians.

International Paediatric Association

Professor G. Fanconi, secretary-general, has circulated the first annual report of this Association. Up to December, 1951, 26 member-associations had been accepted. A conference on abstracting was held in Zurich in October, 1951, and details of the recommendations were published in *Helvetica Paediatrica Acta*, **6**, 5. The World Health Organization has recognized the I.P.A. as a 'non-governmental organization' in official relationship with W.H.O. and has consulted the I.P.A. on various topics. For example, an approach has been made regarding a study on under- and post-graduate education in paediatrics in European countries. Arrangements for the Seventh International Congress of Paediatrics (Cuba, October, 1953) are being discussed by the Executive Board, and it is hoped that some financial assistance may be available to help younger paediatricians to go to the congress.

Thirteenth British Congress of Obstetrics and Gynaecology

This will be held on July 8-11, 1952, in the University of Leeds.

The morning of Wednesday, July 9, is being reserved for a discussion on 'The Place of the Paediatrician in a Maternity Unit'. The opening speakers will be Prof. W. Gaisford and Mr. F. Stosler. The Committee would welcome the attendance of paediatricians in order to join in the discussion after the two opening speakers. Will those who might be interested to attend on this morning of the Congress please get in touch with the Secretary, the 13th British Congress of Obstetrics and Gynaecology, the Hospital for Women, Coventry Place, Leeds, 2, and state whether they are prepared to speak?

Those who wish to attend the Congress only for this day will not be charged a fee. Those who wish to attend the full Congress will be charged the full registration fee.